

XP-002095719 Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy

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Abstract: The total syntheses of epothilones A (1) and B (2) and several analogues thereof are described. The reported strategy relies on a macrolactonization approach and features selective epoxidation of the macrocycle double bond in precursors 3 and 4 (Scheme 1), respectively, as well as high convergency and flexibility. Building blocks 9-12 and 15 were constructed by asymmetric processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogues by a relatively short route. The utilization of intermediate 14, obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone 13 (Scheme 8), in combination with a stereoselective aldol reaction with the modified substrate 69 (Scheme 10) improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

1. Introduction

Epothilones A (1) and B (2) are two architecturally novel natural products recently isolated from the myxobacteria *Sorangium cellulosum* strain 90^{1,2} and possess impressive microtubule binding, affinities and antitumor properties.¹⁻⁴ Their molecular structures have been secured by a combination of spectroscopic and X-ray crystallographic techniques.^{1,2} Interestingly, and despite their structural difference from Taxol, the epothilones were found to bind to the same region on microtubules⁴ and to displace Taxol from its binding site.^{5,6} The higher potency of these new compounds, and their effectiveness against certain drug-resistant tumor cell lines,^{3,4} generated a great deal of excitement among chemists,⁷ biologists, and clinicians. At least five total syntheses⁸⁻¹¹ of epothilone A (1) have already been achieved. The two from these laboratories were based on an olefin metathesis approach⁹ and a macrolactonization approach.¹⁰ The total synthesis of epothilone B (2) and its

analogues has also been reported first by Danishefsky¹² and then by us¹³ in preliminary communications. Here, we report the details of the total synthesis of both epothilones A (1) and B (2) and of a number of analogues of these compounds by our macrolactonization strategy.¹⁰

2. Retrosynthetic Analysis

Scheme 1 outlines the macrolactonization-based retrosynthetic analysis of epothilones A (1) and B (2). Thus, retrosynthetic removal of the epoxide oxygen from 1 and 2 reveals the corresponding Z-olefins, 3 and 4, as potential precursors respectively. The second major retrosynthetic step along this route is the disconnection of the macrocyclic ring at the lactone site, leading to hydroxy acids 5 and 6 as possible key intermediates. Moving further along the retrosynthetic path an aldol-type disconnection allows the generation of keto acid 9 as a common intermediate and aldehydes 7 and 8 as reasonable building blocks for 5 and 6, respectively. Keto acid 9 can be envisioned to arise from an asymmetric allylboration¹⁴ of the corresponding aldehyde, followed by appropriate elaboration of the terminal olefin. The larger intermediates, 7 and 8, can be disconnected by two slightly different ways. The first

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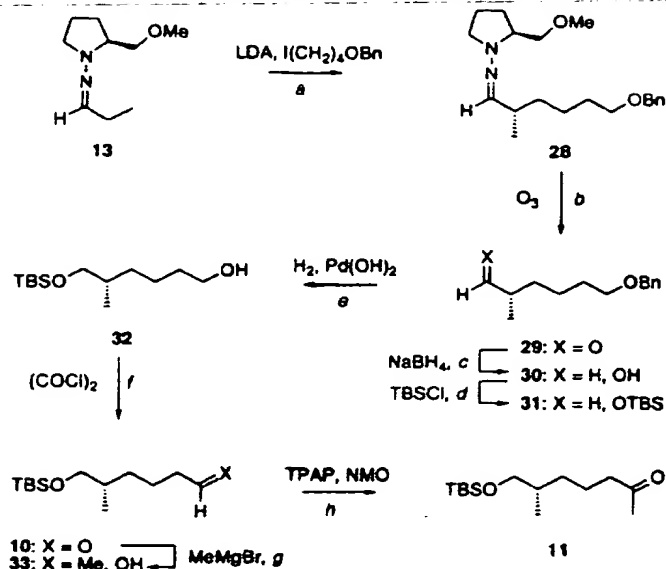
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Scheme 4 Synthesis of Aldehyde 10 and Ketone 11^a

^a Reagents and conditions: (a) 1.1 equiv of LDA, THF, 0 °C, 8 h; then 1.5 equiv of 4-iodo-1-(benzyloxy)butane in THF, at -100 → 0 °C, 6 h, 92% (de > 98% by ¹H NMR); (b) O₃, CH₂Cl₂, -78 °C, 77% or MeI, 60 °C, 5 h; then 3 N aqueous HCl, *n*-pentane, 25 °C, 1 h, 86%; (c) 3.0 equiv of NaBH₄, MeOH, 0 °C, 15 min, 98%; (d) 1.5 equiv of TBSCl, 2.0 equiv of Et₃N, CH₂Cl₂, 0 → 25 °C, 12 h, 95%; (e) H₂, Pd(OH)₂ cat., THF, 50 psi, 25 °C, 15 min, 95%; (f) 2.0 equiv of (COCl)₂, 4.0 equiv of DMSO, 6.0 equiv of Et₃N, CH₂Cl₂, -78 → 0 °C, 1.5 h, 98%; (g) 1.5 equiv of MeMgBr, THF, 0 °C, 15 min, 84%; (h) 1.5 equiv of NMO, 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 4 Å MS, CH₂Cl₂, 25 °C, 45 min, 96%.

with the appropriate stabilized ylide [Ph₃P=C(Me)CHO] in benzene at 80 °C to afford the required (*E*)-α,β-unsaturated-aldehyde 23^{7a,b,h,9} in 98% yield. Addition of (+)-Ipc₂B(allyl)¹⁴ to 23 in ether/pentane at -100 °C gave allylic alcohol 24 in 96% yield (>97% ee by Mosher ester analysis).¹⁷ Protection of the hydroxyl group in 24 as a TBS ether (TBSCl, imidazole, DMF, 99% yield), followed by chemoselective dihydroxylation (OsO₄ cat., NMO)¹⁹ of the terminal olefin (95% yield) and Pb(OAc)₄ cleavage of the resulting diol (98% yield), furnished aldehyde 15 via intermediate 25. Finally, NaBH₄ reduction of 15 (96% yield), followed by iodination (I₂, imidazole, Ph₃P, 89% yield) and phosphonium salt formation (Ph₃P, neat, 100 °C, 98% yield) gave the requisite fragment 12 via the intermediacy of alcohol 26 and iodide 27.

The construction of aldehyde 10 and ketone 11 proceeded from SAMP hydrazone 13 as shown in Scheme 4. Thus, reaction of propionaldehyde with SAMP²⁰ furnished 13, which upon sequential treatment with LDA (THF, 0 °C) and 4-iodo-1-(benzyloxy)butane (THF, -100 → 0 °C) led to compound 28 in 92% yield and >98% de (¹H NMR). Cleavage of the hydrazone moiety by exposure to ozone (CH₂Cl₂, -78 °C, 77% yield) or by treatment with MeI at 60 °C followed by acidic workup (aqueous HCl, 86% yield),²¹ followed by NaBH₄ reduction of the resulting aldehyde (29), furnished alcohol 30 in 98% yield. The latter compound (30) was then silylated with

TBSCl in CH₂Cl₂ in the presence of Et₃N and 4-DMAP to afford silyl ether 31 in 95% yield. Cleavage of the benzyl ether in 31 by hydrogenolysis [H₂, Pd(OH)₂ cat., THF, 50 psi] gave primary alcohol 32 (95% yield), which was smoothly oxidized to the desired aldehyde 10 under Swern conditions²² [(COCl)₂, DMSO, Et₃N, 98% yield]. Addition of MeMgBr to 10 proceeded in 84% yield and was followed by TPAP-NMO oxidation²³ of the resulting secondary alcohol (33) to give the other required building block, ketone 11, in 96% yield.

With the appropriate building blocks at hand, the convergent approach to epothilones A (1) and B (2) could now enter its second phase.

b. Total Synthesis of Epothilone A. The couplings of building blocks 9, 10, and 12 and the total synthesis of epothilone A (1) and its 6*S*,7*R*-diastereoisomers (44 and 45), are shown in Scheme 5. Thus, generation of the ylide from phosphonium salt 12 with sodium bis(trimethylsilyl)amide (NaHMDS), followed by reaction with aldehyde 10 resulted in the formation of the desired *Z*-olefin 34 (*J*_{12,13} = 10.8 Hz, obtained from decoupling experiments) as the predominant product in 77% yield [*Z*:*E* ca. 9:1; the minor isomer (*E*) was removed chromatographically in subsequent steps]. Parenthetically, key intermediate 34 was also prepared by Wittig coupling of phosphonium salt 47 and aldehyde 15 in a reversal of the reacting functionalities of the two fragments as shown in Scheme 6. Thus, alcohol 32 was directly converted to iodide 46 by the action of I₂, imidazole, and Ph₃P (91% yield) and then to phosphonium salt 47 by heating with Ph₃P (91% yield). Generation of the ylide from 47 with equimolar amounts of NaHMDS in THF, followed by reaction with aldehyde 15 yielded *Z*-olefin 34 in 69% and in ca. 9:1 ratio with its *E*-isomer.

Returning to Scheme 5, selective desilylation of the primary hydroxyl group from 34 was achieved by the action of camphorsulfonic acid (CSA) in MeOH:CH₂Cl₂ (1:1),²⁴ leading to hydroxy compound 35 in 86% yield. Oxidation of 35 to aldehyde 7 was then carried out using SO₃-pyr., DMSO, and Et₃N (94% yield).²⁵ With the availability of 7, we were then in a position to investigate its aldol condensation with keto acid 9. It was found that the optimum conditions for this coupling reaction required generation of the dilithio derivative of 9 (1.2 equiv) with 3.0 equiv of lithium diisopropylamide (LDA) in THF (-78 → -40 °C), followed by addition of aldehyde 7 (1.0 equiv), resulting in the formation of a mixture of the desired product 36a and its 6*S*,7*R*-diastereoisomer 36b in ca. 1:1 ratio and in high yield. Despite the lack of stereoselectivity in this reaction, the result was welcome at least with regard to the prospect it provided for the construction of the 6*S*,7*R*-diastereoisomer of epothilones A and B. This mixture was then carried through to the stage of carboxylic acids 38 and 39 (Scheme 5), where it was chromatographically separated to its components. Thus, exposure of 36a,b to excess of TBSOTf and 2,6-lutidine furnished a mixture of tetra-silylated products 37a,b, which was then briefly treated with K₂CO₃ in MeOH²⁶ to afford, after silica gel flash or preparative layer chromatography, carboxylic acids 38 (31% overall yield from 7) and 39 (30% overall yield from 7) (38: *R*_f = 0.61; 39: *R*_f = 0.70, silica gel, 5% MeOH in CH₂Cl₂). The indicated stereochemistry at C7 and C6 in compounds 38 and 39 was assigned later and was based on the successful conversion of 38 to epothilone A (1) as described below.

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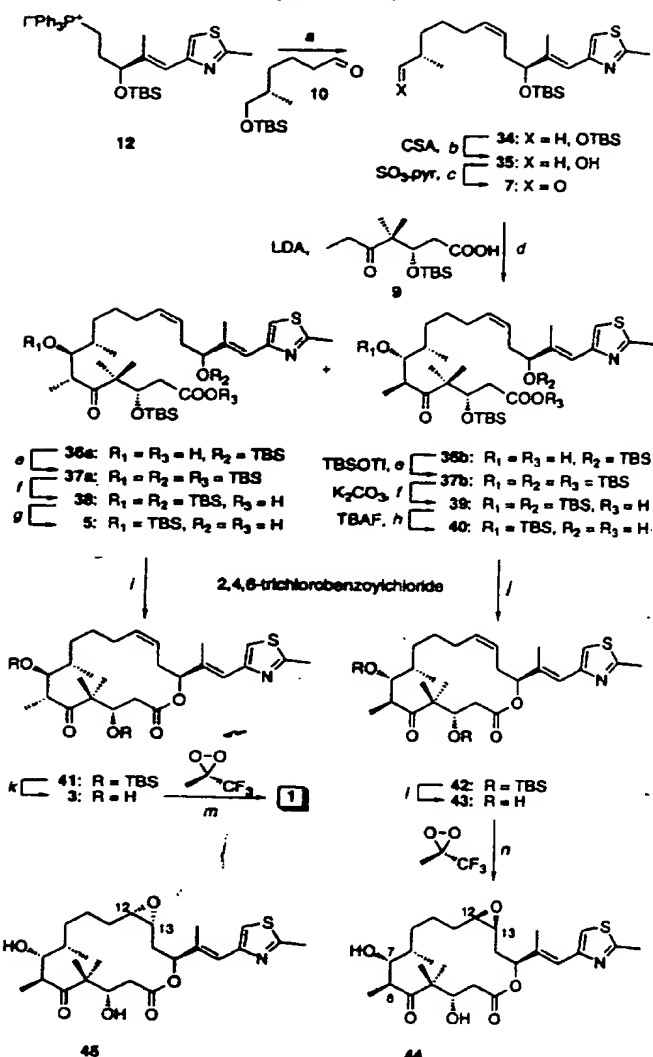
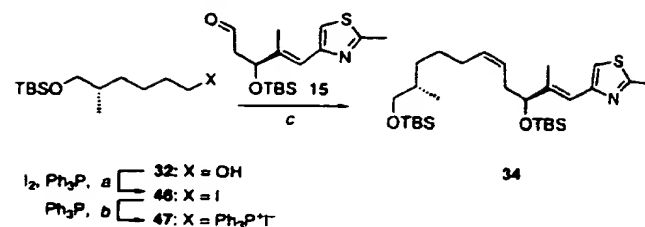
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Scheme 5. Total Synthesis of Epothilone A (1) and Its 6*S*,7*R*-Diastereoisomers (44 and 45)^aScheme 6. Synthesis of Compound 34^a

^a Reagents and conditions: (a) 1.5 equiv of I_2 , 3.0 equiv of imidazole, 1.5 equiv of Ph_3P , $Et_2O:MeCN$ (3:1), 0 °C, 0.5 h, 91%; (b) 1.1 equiv of Ph_3P , neat, 100 °C, 2 h, 91%; (c) 1.2 equiv of $NaHMDS$, THF, 0 °C, 15 min; then add 1.0 equiv of aldehyde 15, 0 °C, 15 min, 69% (Z:E ca. 9:1).

groups from 41 (CF_3COOH , CH_2Cl_2 , 0 °C) furnished diol 3 in 92% yield. Finally, treatment of 3 with methyl(trifluoromethyl)dioxirane²⁸ led cleanly to epothilone A (1) (62% yield) and its α -epoxide epimer (13% yield). The reaction of macrocyclic olefin 3 with *m*CPBA gave a number of other products as described in detailed in the preceding article.²⁹ Synthetic epothilone A (1) was chromatographically purified (preparative thin-layer chromatography, silica gel) and exhibited properties identical to those of an authentic sample (TLC, HPLC, $[\alpha]_D$, IR, 1H and ^{13}C NMR, and HRMS).³⁰

A similar sequence was followed for the synthesis of the 6*S*,7*R*-diastereoisomers 44 and 45 of epothilone A (1) from compound 39 (Scheme 5) via intermediates 40 (82% yield from 39), 42 (85% yield from 40), and 43 (95% yield from 42). Epothilone 44 was obtained as the major product, together with its α -epoxide epimer 45 (87% total yield, ca. 2:1 ratio), from olefinic precursor 43 by methyl(trifluoromethyl)dioxirane epoxidation.²⁸ The epoxide stereochemistry assignments in 44 and 45 are tentative.

c. Total Synthesis of Epothilone B. The first approach to epothilone B (2) was designed with the aim of delivering not only the natural substance but also its 12*S*-diastereoisomer 58 (Scheme 7), which in turn required the generation of both 12*Z*- and 12*E*-olefins. To this end, the ylide generated from phosphonium salt 12 with equimolar amounts of $NaHMDS$ in THF was reacted with ketone 11 to afford a mixture of *Z*- and *E*-olefins 48 (ca. 1:1 ratio) in 73% total yield. This mixture was carried through the sequence to the stage of carboxylic acids 52' and 53' (see Scheme 7 for details), which were chromatographically separable. Carboxylic acid 53' (mixture of geometrical isomers) with the wrong stereochemistry at C6 and C7 (6*S*,7*R*) was abandoned at this stage, whereas the mixture of *Z*- and *E*-isomers 52' with the correct stereochemistry at C6 and C7 (6*R*,7*S*) was taken to the macrolactone stage (compounds 54 and 55) via hydroxy acid 6', by (i) selective desilylation of the C15 hydroxyl group (TBAF, THF, 75% yield) and (ii) Yamaguchi cyclization (37% yield of 54, plus 40% of 55).²⁷ Deprotection of bis(silyl ether) 54 by treatment with CF_3COOH in CH_2Cl_2 afforded diol 4 in 91% yield. Finally, epoxidation of 4 with *m*CPBA in benzene at 3 °C gave epothilone B (2) together with its α -epoxide epimer 57 in 66% total yield and

^a Reagents and conditions: (a) 1.2 equiv of 12, 1.2 equiv of $NaHMDS$, THF, 0 °C, 15 min, then add 1.0 equiv of aldehyde 10, 0 °C, 15 min, 77% (Z:E ca. 9:1); (b) 1.0 equiv of CSA portionwise over 1 h, $CH_2Cl_2:MeOH$ (1:1), 0 → 25 °C, 0.5 h, 86%; (c) 2.0 equiv of $SO_3 \cdot pyr.$, 10.0 equiv of DMSO, 5.0 equiv of Et_3N , CH_2Cl_2 , 25 °C, 0.5 h, 94%; (d) 3.0 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of 9 in THF, -78 → -40 °C, 0.5 h; then 1.0 equiv of 7 in THF at -78 °C, high yield of 36a and its 6*S*,7*R*-diastereoisomer 36b (ca. 1:1 ratio); (e) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2 , 0 °C, 2 h; (f) 2.0 equiv of K_2CO_3 , MeOH, 25 °C, 15 min, 31% of 38 and 30% of 6*S*,7*R*-diastereoisomer 39 from 7; (g) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 78%; (h) same as g, 82%; (i) 5.0 equiv of 2,4,6-trichlorobenzoyl chloride, 6.0 equiv of Et_3N , THF, 25 °C, 15 min; then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on 5), 25 °C, 0.5 h, 90%; (j) same as i, 85%; (k) 20% CF_3COOH (by volume) in CH_2Cl_2 , 0 °C, 1 h, 92%; (l) same as k, 95%; (m) methyl(trifluoromethyl)dioxirane, MeCN, 0 °C, 75% (ca. 5:1 ratio of diastereoisomers, see ref 27); (n) same as m, 87% (44:45 ca. 2:1 ratio of diastereoisomers, tentative stereochemistry).

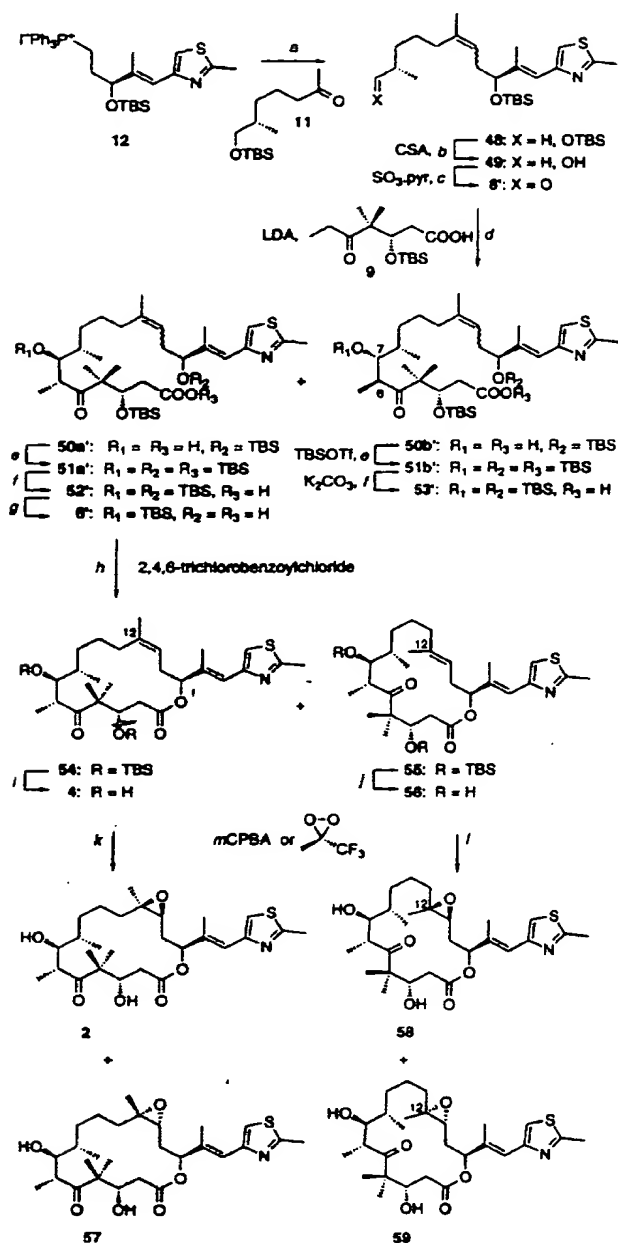
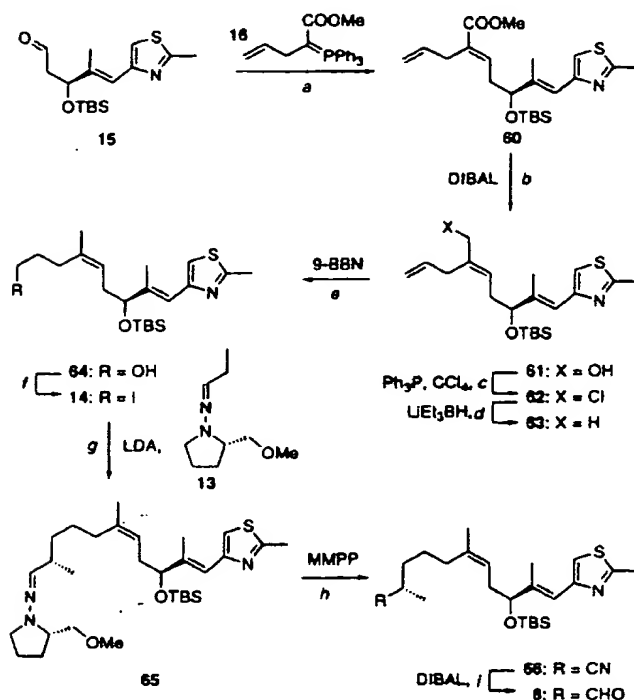
At this stage, it was necessary to selectively remove the TBS group from the allylic hydroxyl group of 38, so as to allow macrolactonization of the *seco*-acid substrate (5). This goal was achieved by treatment of 38 with tetra-*n*-butylammonium fluoride (TBAF) in THF at 25 °C, generating the desired hydroxy acid 5 in 78% yield. The key macrolactonization reaction of 5 was carried out using the Yamaguchi method²⁷ (2,4,6-trichlorobenzoyl chloride, Et_3N , 4-DMAP) at 25 °C, affording compound 41 in 90% yield. Removal of both TBS

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Scheme 7. Total Synthesis of Epothilone B (2) and Analogues^aScheme 8. Stereoselective Synthesis of Aldehyde 8 for Epothilone B (2)^a

^a Reagents and conditions: (a) 1.5 equiv of 16, benzene, reflux 5 h, 95%; (b) 3.0 equiv of DIBAL, THF, -78 °C, 2 h, 98%; (c) 2.0 equiv of Ph₃P, CCl₄, reflux, 24 h, 83%; (d) 2.0 equiv of LiEt₃BH, THF, 0 °C, 1 h, 99%; (e) 1.2 equiv of 9-BBN, THF, 0 °C, 2 h, 91%; (f) 1.5 equiv of I₂, 3.0 equiv of imidazole, 1.5 equiv of Ph₃P, Et₃O:MeCN (3:1) 0 °C, 0.5 h, 92%; (g) 1.5 equiv of 13, 1.5 equiv of LDA, THF, 0 °C, 8 h; then 1.0 equiv of 14 in THF, -100 → -20 °C, 10 h, 70%; (h) 2.5 equiv of monoperoxyphthalic acid, magnesium salt (MMPP), MeOH:phosphate buffer pH7 (1:1), 0 °C, 1 h, 80%; (i) 2.0 equiv of DIBAL, toluene, -78 °C, 1 h, 82%.

ca. 5:1 ratio (¹H NMR), while the use of dimethyldioxirane,³¹ first reported by Danishefsky,^{8a,12} gave 2 and 27 in 75% total yield in the same ratio (ca. 5:1 in favor of 2). Epoxidation of 4 with methyl(trifluoromethyl)dioxirane²⁸ in CH₃CN at 0 °C improved the yield of epothilone B (2) and its α-epimer 57 to 85% but did not significantly change the diastereoselectivity of the reaction. Epothilone B (2) was purified by silica gel preparative layer chromatography and exhibited identical properties (TLC, HPLC, [α]_D, IR, ¹H and ¹³C NMR, and HRMS) with those of an authentic sample.³⁰

By the same sequence, and in similar yields, the macrocycle 55 containing the *E*-endocyclic double bond (Scheme 7) was converted to the 12*S*-epimeric epothilone B 58 and its α-epoxy epimer 59 via dihydroxy macrocyclic compound 56 [epoxidation with methyl(trifluoromethyl)dioxirane].²⁸ The stereochemistry of epoxides 58 and 59 was tentatively assigned by comparisons with the corresponding epothilone A epoxides whose stereochemistry was determined by NMR spectroscopy and molecular dynamics computations and molecular modeling as described in the preceding article²⁹ (see also Supporting Information for ¹H-¹H NOESY and ¹H-¹H COSY).

To improve the efficiency of the route to epothilone B (2), a more stereoselective total synthesis was devised and executed as follows. Scheme 8 addresses the stereoselective construction of intermediate 8 with the 12*Z*-geometry. Thus, condensation of the stabilized ylide 16 [obtained from 4-bromo-1-butene by (i) phosphonium salt formation, (ii) anion formation with

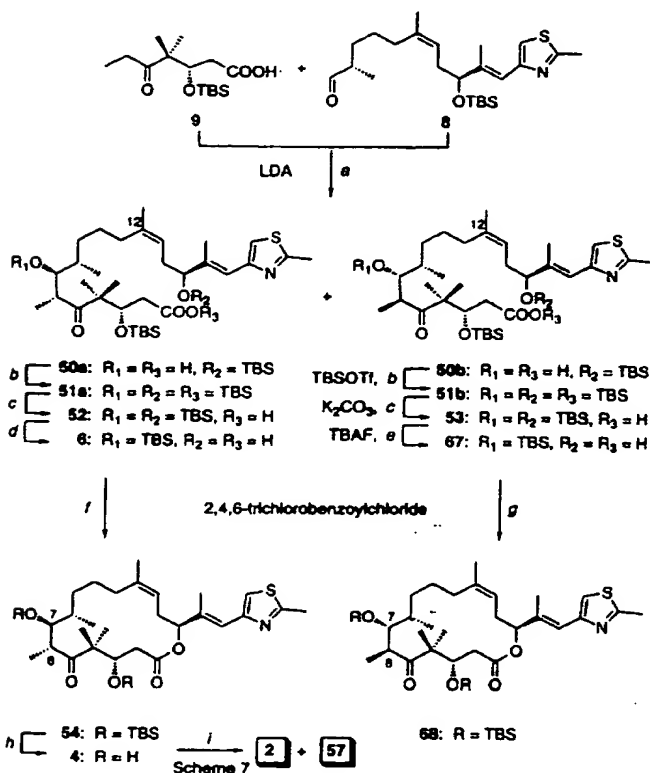
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NaHMDS, and (iii) quenching with MeOC(O)Cl ³² with aldehyde 15 proceeded smoothly to afford olefinic compound 60 in 95% yield and as a single isomer. Reduction of the methyl ester in 60 with DIBAL resulted in the formation of allylic alcohol 61 (98% yield), which was deoxygenated by first reacting it with $\text{Ph}_3\text{P}-\text{CCl}_4$ and then with LiEt_3BH ,³³ to afford the desired trisubstituted 12Z-olefin 63, via chloride 62, in 82% overall yield. The latter compound 63 was regioselectively hydroborated with 9-BBN and converted to the primary alcohol 64 (91%), which was then treated with I_2 -imidazole- Ph_3P to afford iodide 14 (92% yield). This iodide was then used in an Enders alkylation reaction with SAMP hydrazone 13 to give compound 65 as a single isomer (^1H NMR) and in 70% yield. Treatment of hydrazone 65 with monoperoxyphthalic acid magnesium salt (MMP) in MeOH :phosphate pH 7 buffer (1:1)^{20c,34} resulted in clean conversion to nitrile 66 (80% yield), which formed aldehyde 8 (82% yield) upon exposure to DIBAL at -78°C in toluene solution.

The homogeneous aldehyde 8 was converted to epothilone B (2) by the sequence depicted in Scheme 9. Thus, condensation of the dianion of 9 with 8 as before (Scheme 7), produced two diastereoisomers, 50a (6R,7S stereoisomer) and 50b (6S,7R stereoisomer), in high yield and in ca. 1.3:1.0 ratio (50a:50b). This mixture was carried through the indicated sequence to carboxylic acids 52 (32% overall yield from 8) and 53 (28% overall yield from 8), which were separated by silica gel preparative layer or flash column chromatography and taken individually further along the sequence as described for the corresponding stereoisomeric mixtures shown in Scheme 7. Thus, 52 was selectively deprotected with TBAF to afford hydroxy acid 6 (73% yield), which was then cyclized to macrolactone 54 in 77% yield by the Yamaguchi method.²⁷ The conversion of 54 to epothilone B (2) and its α -epoxide epimer 57 has already been described above (Scheme 7).

In an effort to improve the diastereoselectivity of the aldol condensation between C1-C6 and C7-C15 fragments, the following chemistry was explored (Scheme 10). Thus, ketone 69 [prepared from ketone 20 (Scheme 2) by selective reduction, followed by silylation] was converted to its enolate with stoichiometric amounts of LDA, and reacted with aldehyde 8 (Z-isomer), affording coupling products 70 and 71 in 85% total yield and ca. 3:1 ratio, with the desired compound 70 predominating as proven by its conversion to 52 and epothilone B (2). Thus, chromatographic purification (silica gel, 20% ether in hexanes) led to 70, which was efficiently transformed to the previously synthesized intermediate 52 (Scheme 9) as follows. The newly generated hydroxyl group in 70 was silylated with TBSOTf-2,6-lutidine to furnish 72 (96% yield), which was then selectively desilylated at the primary position by the mild action of camphorsulfonic acid (CSA) in $\text{MeOH}-\text{CH}_2\text{Cl}_2$, leading to 73 (85%). Finally, sequential oxidation of the primary alcohol with $(\text{COCl})_2-\text{DMSO}-\text{Et}_3\text{N}$ (95% yield) and $\text{NaClO}_2-\text{NaH}_2\text{PO}_4$ (90% yield) led to hydroxy acid 52 via aldehyde 74. The conversion of 52 to 2 has already been described above (Scheme 9). This sequence represents a stereoselective and highly efficient synthesis of epothilone B (2) and opens the way for the construction of further analogues within this important family of microtubule binding agents.

Scheme 9. First Stereoselective Total Synthesis of Epothilone B (2)^a



^a Reagents and conditions: (a) 3.0 equiv of 9 in THF, -78°C , 0.5 h, then 1.0 equiv of 8 in THF at -78°C , high yield of 50a and 6S,7R-diastereoisomer 50b (ca. 1.3:1.0 ratio of diastereoisomers); (b) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2 , 0°C , 2 h; (c) 2.0 equiv of K_2CO_3 , MeOH , 25°C , 15 min, 32% of 52 and 28% of 6S,7R-diastereoisomer 53 from 8; (d) 6.0 equiv of TBAF, THF, 25°C , 8 h, 73%; (e) same as d, 71%; (f) 5.0 equiv of 2,4,6-trichlorobenzoyl chloride, 6.0 equiv of Et_3N , THF, 25°C , 15 min, then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on 6), 25°C , 12 h, 77%; (g) same as f, 76%; (h) 20% CF_3COOH (by volume) in CH_2Cl_2 , 0°C , 1 h, 91%; (i) see Scheme 7.

4. Conclusion

The chemistry described in this article defines a concise strategy for the construction of epothilones A (1) and B (2) based on a macrolactonization strategy, and which enjoys convergency and flexibility for structural diversity. It is expected that the numerous intermediates and structural analogues included herein, as well as several new ones currently under construction, will play a crucial role in elucidating structure-activity relationships of these new substances and in determining their relevance to cancer chemotherapy. Indeed, independent reports from the Danishefsky^{8b,12} and from these laboratories¹³ demonstrated impressive tubulin binding affinities and cytotoxicities for some of these compounds. Further details on the biological actions of these and other compounds will be published elsewhere.

Experimental Section

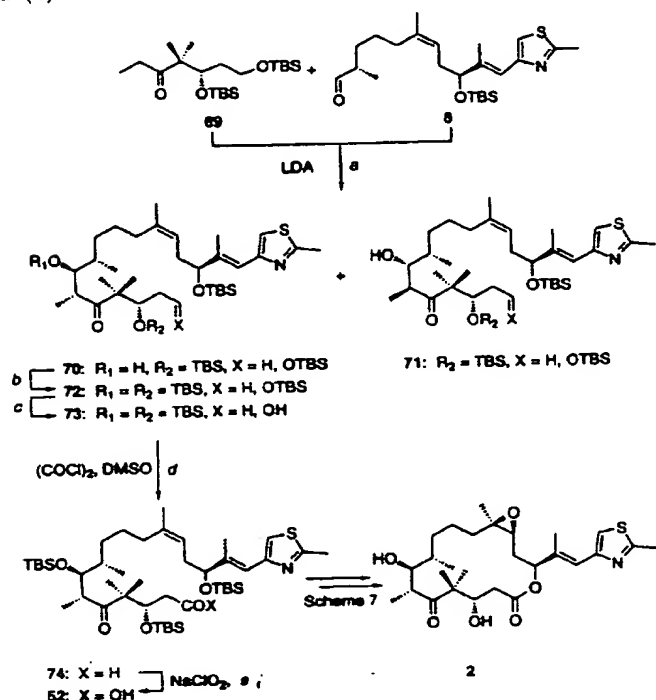
General Techniques. See preceding paper.²⁹

Alcohol 18. Allylboration of Keto Aldehyde 17. Aldehyde 17¹⁶ (16.0 g, 0.125 mol) was dissolved in ether (400 mL) and cooled to -100°C . To this solution was added (+)-diisopinocampheylallylborane (800 mL, 0.15 M in pentane, 0.125 mol, 1.0 equiv) by cannulation during 45 min. [(+)-Diisopinocampheylallylborane in pentane was typically prepared by the adaptation of the original method reported by Brown.¹⁴ Allylmagnesium bromide (66.0 mL, 1 M solution in ether,

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Scheme 10. Second Stereoselective Synthesis of Epothilone B (2)^a

^a Reagents and Conditions: (a) 1.2 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of 69 in THF, -78 °C, 1 h; then 1.0 equiv of 8 in THF at -78 °C, 85% of 70 and 6S,7R-diastereoisomer 71 (ca. 3:1 ratio); (b) 1.2 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH₂Cl₂, 0 °C, 2 h, 96%; (c) 1.0 equiv of CSA portionwise over 1 h, CH₂Cl₂:MeOH (1:1), 0 → 25 °C, 0.5 h, 85%; (d) 2.0 equiv of (COCl)₂, 4.0 equiv of DMSO, 6.0 equiv of Et₃N, CH₂Cl₂, -78 → 0 °C, 1.5 h, 95%; (e) 3.0 equiv of NaClO₂, 4.0 equiv of 2-methyl-2-butene, 1.5 equiv of NaH₂PO₄, BuOH:H₂O (5:1), 25 °C, 2 h, 90%.

0.066 mol) was added dropwise to a well-stirred solution of (-)-*B*-methoxydiisopinocampheylborane (20.9 g, 0.066 mol) in ether (400 mL) at 0 °C. After the completion of the addition, the reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was extracted with pentane (3 × 400 mL) under argon, and stirring was discontinued to allow precipitation of the magnesium salts. The clear pentane solution was cannulated into another flask using a double-ended needle through a Kramer filter and used without further purification. After the addition was complete, the mixture was stirred at the same temperature for 30 min. Methanol (20 mL) was added at -100 °C, and the reaction mixture was allowed to reach room temperature. To this solution was added saturated aqueous NaHCO₃ solution (200 mL), followed by H₂O₂ (80 mL of 50% solution in H₂O), and the reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was extracted with EtOAc (3 × 200 mL), and the organic extracts were combined, washed with saturated aqueous NH₄Cl solution (100 mL), and dried (Na₂SO₄). Evaporation of the solvents followed by flash column chromatography (silica gel, 3% acetone in CH₂Cl₂) resulted in pure alcohol 18 (14.6 g, 74%). 18: colorless oil; *R*_f = 0.20 (silica gel, 3% acetone in CH₂Cl₂); [α]_D²⁰ -4.0 (c 1.5, CHCl₃); IR (thin film) *ν*_{max} 3492, 2976, 2939, 1699, 1641, 1469, 1379, 1087, 1020, 990, 973, 914 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.85–5.80 (m, 1 H, CH=CH₂), 5.11–5.07 (m, 2 H, CH=CH₂), 3.73 (dd, *J* = 10.5, 2.0 Hz, 1 H, CHOH), 2.54–2.40 (m, 3 H), 2.25–2.18 (m, 1 H), 2.09–1.96 (m, 1 H), 1.14 (s, 3 H, C(CH₃)₂), 1.10 (s, 3 H, C(CH₃)₂), 0.99 (t, *J* = 7.0 Hz, 3 H, CH₃CH₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 217.2, 135.6, 117.7, 75.5, 51.2, 36.4, 31.3, 21.8, 19.5, 7.8; FAB HRMS (NBA/Na) *m/z* 193.1200, *M* + Na⁺ calcd for C₁₀H₁₈O₂ 193.1204.

Ketone 19. Silylation of Alcohol 18. Alcohol 18 (11.0 g, 0.0647 mol) was dissolved in CH₂Cl₂ (200 mL), the solution was cooled at -78 °C, and 2,6-lutidine (10.5 mL, 0.0906 mol, 1.4 equiv) was added. After being stirred for 5 min at that temperature, *tert*-butyldimethylsilyl triflate (19.3 mL, 0.0841 mol, 1.3 equiv) was added dropwise and the

reaction mixture was allowed to stir at -78 °C for 45 min, after which time no starting material was detected by TLC. Saturated aqueous NH₄Cl solution (30 mL) was added, and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were dried (MgSO₄) and filtered through Celite, and the solvents were removed under reduced pressure. Purification by flash column chromatography (silica gel, 2 → 10% ether in hexanes) gave pure 19 (18.0 g, 98%); *R*_f = 0.75 (silica gel, 20% ether in hexanes); [α]_D²⁰ +2.6 (c 0.8, CHCl₃); IR (thin film) *ν*_{max} 2935, 1705, 1467, 1362, 1254, 1089, 911, 836, 775 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.78–5.71 (m, 1 H, CH=CH₂), 5.01–4.94 (m, 2 H, CH=CH₂), 3.97 (dd, *J* = 6.2, 5.2 Hz, 1 H, CHOSi), 2.54 (dq, *J* = 14.3, 7.2 Hz, 1 H, CH₂CH₃), 2.44 (dq, *J* = 14.2, 7.1 Hz, 1 H, CH₂CH₃), 2.21–2.16 (m, 1 H, CH₂CH=CH₂), 2.14–2.08 (m, 1 H, CH₂CH=CH₂), 1.10 (s, 3 H, C(CH₃)₂), 1.07 (s, 3 H, C(CH₃)₂), 0.98 (t, *J* = 7.1 Hz, 3 H, CH₃CH₂), 0.87 (s, 9 H, Si(CH₃)₃), 0.05 (s, 3 H, Si(CH₃)₂), 0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 215.9, 136.2, 116.5, 76.7, 52.9, 39.0, 31.9, 26.0, 22.4, 20.1, 18.2, 7.7, -3.6, -4.4.

Keto Aldehyde 20. Ozonolysis of Ketone 19. Alkene 19 (2.84 g, 10 mmol) was dissolved in CH₂Cl₂ (25 mL, 0.4 M), and the solution was cooled to -78 °C. Oxygen was bubbled through for 2 min, after which time ozone was passed through until the reaction mixture adopted a blue color (ca. 30 min). The solution was then purged with oxygen for 2 min at -78 °C (disappearance of blue color) and Ph₃P (3.16 g, 12.0 mmol, 1.2 equiv) was added. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature and stirred for an additional 1 h. The solvent was removed under reduced pressure, and the mixture was purified by flash column chromatography (silica gel, 25% ether in hexanes) to provide pure keto aldehyde 20 (2.57 g, 90%); *R*_f = 0.45 (silica gel, 20% ether in hexanes); [α]_D²⁰ -1.9 (c 4.0, CHCl₃); IR (thin film) *ν*_{max} 2935, 2858, 1707, 1467, 1388, 1255, 1093, 1004, 837, 777 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.73 (dd, *J* = 2.1, 2.0 Hz, CHO), 4.55 (dd, *J* = 6.0, 4.5 Hz, 1 H, CHOSi), 2.59–2.44 (m, 4 H, CH₂CH₃, CH₂CH=O), 1.13 (s, 3 H, C(CH₃)₂), 1.09 (s, 3 H, C(CH₃)₂), 1.00 (t, *J* = 7.0 Hz, 3 H, CH₃CH₂), 0.85 (s, 9 H, (CH₃)₃Si), 0.06 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 215.3, 200.9, 71.3, 52.3, 48.5, 31.9, 25.8, 21.3, 20.4, 18.0, 7.5, -4.4, -4.9; FAB HRMS (NBA/Na) *m/z* 309.1854, *M* + Na⁺ calcd for C₁₃H₂₀O₃Si 309.1862.

Keto Acid 9. Oxidation of Keto Aldehyde 20. Aldehyde 20 (2.36 g, 10 mmol), BuOH (50 mL, 0.2 M), isobutylene (20 mL, 2 M solution in THF, 40 mmol, 4.0 equiv), H₂O (10 mL), NaClO₂ (2.71 g, 33.0 mmol, 3.0 equiv), and NaH₂PO₄ (1.80 g, 15.0 mmol, 1.5 equiv) were combined and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, 50% ether in hexanes) to produce pure keto acid 9 (2.81 g, 93%); *R*_f = 0.12 (silica gel, 20% ether in hexanes); [α]_D²⁰ +16.1 (c 1.0, CHCl₃); IR (thin film) *ν*_{max} 3334, 2858, 1710, 1467, 1254, 1093, 834 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.46 (dd, *J* = 7.0, 3.6 Hz, 1 H, CHOSi), 2.64–2.34 (m, 3 H, CH₂CH₃, CH₂COOH), 2.32 (q, *J* = 7.0 Hz, 1 H, CH₂CH₃), 1.13 (s, 3 H, C(CH₃)₂), 1.11 (s, 3 H, C(CH₃)₂), 0.99 (t, *J* = 7.0 Hz, 3 H, CH₃CH₂), 0.83 (s, 9 H, (CH₃)₃Si), 0.04 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 215.1, 178.2, 73.4, 52.4, 39.2, 31.6, 25.8, 20.8, 20.5, 18.0, 7.6, -4.5, -5.0; FAB HRMS (NBA/Na) *m/z* 303.1996, *M* + H⁺ calcd for C₁₃H₂₀O₃Si 303.1992.

Aldehyde 22. Reduction of Ester 21. Ethyl ester 21¹⁵ (5.5 g, 0.306 mol) was dissolved in CH₂Cl₂ (1 L) and cooled to -78 °C. DIBAL (490.0 mL, 1 M solution in CH₂Cl₂, 0.4896 mol, 1.6 equiv) was added dropwise via a cannula while the temperature of the reaction mixture was maintained at -78 °C. After the addition was complete, the reaction mixture was stirred at the same temperature until completion was verified by TLC (ca. 1 h). Methanol (100 mL) was added at -78 °C and was followed by addition of EtOAc (100 mL) and saturated aqueous NH₄Cl solution (300 mL). The quenched reaction mixture was allowed to warm to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 → 20% ether in hexanes) furnished the desired aldehyde 22 (33.6 g, 90%); *R*_f =

0.68 (silica gel, ether); IR (thin film) ν_{\max} 3095, 2828, 1695, 1485, 1437, 1378, 1334, 1178, 1129, 1011 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.96 (s, 1 H, CHO), 8.0 (s, 1 H, SCH=C), 2.77 (s, 3 H, N=C(S)CH₃); ^{13}C NMR (125.7 MHz, CDCl_3) δ 184.2, 167.5, 154.8, 128.0, 19.1; FAB HRMS (NBA/NaI) m/e 149.9992, $M + \text{Na}^+$ calcd for $\text{C}_3\text{H}_5\text{NOS}$ 149.9990.

Aldehyde 23. Aromatic aldehyde 22 (31.1 g, 0.245 mol) was dissolved in benzene (500 mL), and 2-(triphenylphosphoranylidene)-propionaldehyde (90.0 g, 0.282 mol, 1.15 equiv) was added. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca. 2 h). Evaporation of the solvent under reduced pressure followed by flash column chromatography (10 → 90% ether in hexanes) produced the desired aldehyde 23 (40.08 g, 98%): R_f = 0.78 (silica gel, ether); IR (thin film) ν_{\max} 3089, 1675, 1624, 1190, 1141, 1029, 947.6, 881 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.57 (s, 1 H, CHO), 7.46 (s, 1 H), 7.26 (s, 1 H), 2.77 (s, 3 H, N=C(S)CH₃), 2.20 (s, 3 H, CH=C(CHO)CH₃); ^{13}C NMR (125.7 MHz, CDCl_3) δ 195.3, 165.7, 151.9, 140.9, 138.2, 122.6, 19.2, 10.9; FAB HRMS (NBA) m/e 168.0481, $M + \text{H}^+$ calcd for $\text{C}_8\text{H}_9\text{NOS}$ 168.0483.

Alcohol 24. Allylboration of Aldehyde 23. Aldehyde 23 (20.0 g, 0.120 mol) was dissolved in anhydrous ether (400 mL), and the solution was cooled to -100°C . (+)-Diisopinocampheylallylborane (1.5 equiv in pentane, prepared from 60.0 g of (–)-Ipc₂BOMe and 1.0 equiv of allylmagnesium bromide according to the method described for the synthesis of alcohol 18),¹⁴ was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol (40 mL) was added at -100°C , and the reaction mixture was allowed to warm to room temperature. Aminoethanol (72.43 mL, 1.2 mol, 10.0 equiv) was added, and stirring was continued for 15 h. The workup procedure was completed by the addition of saturated aqueous NH_4Cl solution (200 mL), extraction with EtOAc (4 × 100 mL), and drying of the combined organic layers with MgSO_4 . Filtration followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol 24 (24.09 g, 96%): R_f = 0.37 (60% ether in hexanes); $[\alpha]_D^{20}$ -20.2 (c 1.0, CHCl_3); IR (thin film) ν_{\max} 3357, 2923, 1642, 1505, 1437, 1322, 1186, 1018, 914, 878 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.81 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH₃), 5.87–5.79 (m, 1 H, CH=CH₂), 5.02 (d, J = 17.1 Hz, 1 H, CH=CH₂), 4.97 (d, J = 10.3 Hz, 1 H, CH=CH₂), 4.12 (dd, J = 7.8, 5.0 Hz, 1 H, CHOH), 3.8 (bs, 1 H, OH), 2.59 (s, 3 H, N=C(S)CH₃), 2.31 (dd, J = 7.0, 6.5 Hz, 2 H, CH₂=CHCH₂), 1.91 (s, 3 H, CH=CCH₃); ^{13}C NMR (150.9 MHz, CDCl_3) δ 164.5, 152.5, 141.8, 134.8, 118.7, 117.1, 115.1, 76.3, 39.8, 18.8, 14.1; FAB HRMS (NBA) m/e 210.0956, $M + \text{H}^+$ calcd for $\text{C}_{11}\text{H}_{13}\text{NOS}$ 210.0953.

Compound 25. Silylation of Alcohol 24. Alcohol 24 (7.0 g, 0.033 mol) was dissolved in DMF (35 mL, 1.0 M), the solution was cooled to 0°C , and imidazole (3.5 g, 0.050 mol, 1.5 equiv) was added. After stirring for 5 min, *tert*-butyldimethylsilyl chloride (6.02 g, 0.040 mol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0°C for 45 min, and then at 25°C for 2.5 h, after which time no starting alcohol was detected by TLC. Methanol (2 mL) was added at 0°C , and the solvent was removed under reduced pressure. Ether (100 mL) was added followed by saturated aqueous NH_4Cl solution (20 mL), the organic phase was separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic solution was dried (MgSO_4) and filtered over Celite, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 10 → 20% ether in hexanes) provided pure 25 (10.8 g, 99%): R_f = 0.70 (40% ether in hexanes); $[\alpha]_D^{20}$ $+1.39$ (c 3.0, CHCl_3); IR (thin film) ν_{\max} 2931, 2060, 1496, 1460, 1249, 1173, 1073, 908, 837, 779 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.80–5.75 (m, 1 H, CH=CH₂), 5.03 (ddd, J = 17.1, 5.1, 1.5 Hz, 1 H, CH=CH₂), 4.99 (ddd, J = 10.2, 2.1, 0.9 Hz, 1 H, CH=CH₂), 4.14 (dd, J = 6.6, 6.1 Hz, 1 H, CHOH), 2.69 (s, 3 H, N=C(S)CH₃), 2.37–2.32 (m, 1 H, CH₂=CHCH₂), 2.31–2.25 (m, 1 H, CH₂=CHCH₂), 1.99 (s, 3 H, CH=CCH₃), 0.88 (s, 9 H, Si(CH₃)₃), 0.05 (s, 3 H, Si(CH₃)₂), 0.00 (s, 3 H, Si(CH₃)₂); ^{13}C NMR (150.9 MHz, CDCl_3) δ 165.2, 153.9, 142.9, 136.2, 119.7, 117.4, 115.9, 79.3, 42.1, 6.7, 20.1, 19.0, 14.8, -3.8 , -4.1 ; FAB HRMS (NBA) m/e 324.1804, $M + \text{H}^+$ calcd for $\text{C}_{17}\text{H}_{23}\text{NOSSi}$ 324.1817.

Aldehyde 15. Dihydroxylation of Olefin 25 and 1,2 Glycol Cleavage. Olefin 25 (16.7 g, 51.6 mmol) was dissolved in THF/ BuOH (1:1, 500 mL) and H_2O (50 mL). 4-Methylmorpholine *N*-oxide (NMO) (7.3 g, 61.9 mmol, 1.2 equiv) was added at 0°C , followed by OsO_4 (5.2 mL, solution in BuOH 1.0 mol %, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0°C and then for 12 h at 25°C . After completion of the reaction, Na_2SO_3 (5.0 g) was added at 0°C , followed by H_2O (100 mL). Stirring was continued for another 30 min, and then ether (1 L) was added, followed by saturated aqueous NaCl solution (2 × 100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic extracts were dried (MgSO_4) and filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, ether → EtOAc) provided 17.54 g (95%) of the expected 1,2-diol as a 1:1 mixture of diastereoisomers: R_f = 0.55 (silica gel, EtOAc); IR (thin film) ν_{\max} 3380, 2931, 2856, 1656, 1505, 1465, 1460, 1254, 1187, 1073, 908, 837, 777 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.90 and 6.88 (singlets, 1 H total, SCH=C), 6.52 and 6.47 (singlets, 1 H total, CH=CCH₃), 4.44–4.39 (m, 1 H), 3.95–3.84 (m, 1 H), 3.81–3.72 and 3.63–3.34 (m, 4 H total), 2.66 and 2.65 (singlets, 3 H total, N=C(S)CH₃), 1.96 and 1.95 (singlets, 3 H total), 1.82–1.75 and 1.69–1.56 (m, 2 H total), 0.87 and 0.86 (singlets, 9 H total, Si(CH₃)₃), 0.08 and -0.01 (singlets, 3 H total, Si(CH₃)₂), 0.07 and 0.10 (singlets, 3 H total, Si(CH₃)₂); ^{13}C NMR (125.7 MHz, CDCl_3) δ 164.6, 164.5, 152.8, 152.4, 141.6, 141.5, 119.4, 118.4, 115.3, 115.2, 78.0, 75.4, 70.4, 68.8, 66.8, 66.5, 38.9, 38.7, 25.7, 19.0, 18.9, 18.0, 17.9, 14.6, 13.5, -4.6 , -4.8 , -5.2 , -5.4 ; FAB HRMS (NBA/NaI) m/e 380.1699, $M + \text{Na}^+$ calcd for $\text{C}_{17}\text{H}_{31}\text{NO}_2\text{SSi}$ 380.1692.

The diol obtained from 25 as described above (5.2 g, 14.5 mmol) was dissolved in EtOAc (150 mL) and cooled to 0°C . $\text{Pb}(\text{OAc})_4$ (8.1 g, 95% purity, 18.3 mmol, 1.2 equiv) was then added portionwise over 10 min, and the mixture was vigorously stirred for 15 min at 0°C . After completion of the reaction, the mixture was filtered through silica gel and washed with 60% ether in hexanes. The solvents were then removed under reduced pressure providing pure aldehyde 15 (4.7 g, 98%): R_f = 0.76 (silica gel, 60% ether in hexanes); $[\alpha]_D^{20}$ -20.3 (c 1.4, CHCl_3); IR (thin film) ν_{\max} 2931, 2856, 1726, 1504, 1466, 1389, 1254, 1182, 1087, 999, 839, 784 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.69 (dd, J = 2.7, 2.2 Hz, 1 H, CHO), 6.86 (s, 1 H, SCH=C), 6.48 (s, 1 H, CH=CCH₃), 4.60 (dd, J = 8.2, 3.9 Hz, 1 H, CHOSi), 2.64 (ddd, J = 15.5, 8.3, 2.9 Hz, 1 H, CHOCH₂), 2.59 (s, 3 H, N=C(S)CH₃), 2.41 (ddd, J = 15.5, 4.0, 2.0 Hz, 1 H, CHOCH₂), 1.95 (s, 3 H, CH=CCH₃), 0.79 (s, 9 H, Si(CH₃)₃), 0.00 (s, 3 H, Si(CH₃)₂), -0.06 (s, 3 H, Si(CH₃)₂); ^{13}C NMR (125.7 MHz, CDCl_3) δ 201.0, 164.5, 152.4, 140.3, 119.0, 115.8, 73.7, 49.9, 25.6, 18.9, 17.9, 13.9, -4.8 , -5.4 ; FAB HRMS (NBA) m/e 326.1615, $M + \text{H}^+$ calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_2\text{SSi}$ 326.1610.

Alcohol 26. Reduction of Aldehyde 15. A solution of aldehyde 15 (440 mg, 1.35 mmol) in MeOH (13 mL) was treated with NaBH_4 (74 mg, 2.0 mmol, 1.5 equiv) at 0°C for 15 min. The solution was diluted with ether (100 mL), and then saturated aqueous NH_4Cl solution (5 mL) was carefully added. The organic phase was washed with brine (10 mL), dried (MgSO_4), and concentrated. Flash column chromatography (silica gel, 60% ether in hexanes) gave alcohol 26 (425 mg, 96%) as a colorless oil. 26: R_f = 0.52 (silica gel, 60% ether in hexanes); $[\alpha]_D^{20}$ -29.4 (c 0.8, CHCl_3); IR (thin film) ν_{\max} 3362, 2950, 2856, 1656, 1505, 1466, 1362, 1254, 1186, 1075, 839, 777 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.86 (s, 1 H, SCH=C), 6.40 (s, 1 H, CH=CCH₃), 4.30 (dd, J = 7.6, 5.3 Hz, 1 H, CHOSi), 3.69–3.59 (m, 2 H, CH₂OH), 3.15 (s, 1 H, OH), 2.61 (s, 3 H, N=C(S)CH₃), 1.92 (s, 3 H, CH=CCH₃), 1.82–1.76 (m, 1 H, CH₂CH₂OH), 1.73–1.67 (m, 1 H, CH₂CH₂OH), 0.82 (s, 9 H, Si(CH₃)₃), 0.02 (s, 3 H, Si(CH₃)₂), -0.05 (s, 3 H, Si(CH₃)₂); ^{13}C NMR (150.9 MHz, CDCl_3) δ 164.3, 152.7, 141.6, 118.5, 115.1, 76.6, 59.6, 38.3, 25.8, 18.9, 18.0, 14.0, -4.8 , -5.4 ; FAB HRMS (NBA/CsI) m/e 460.0727, $M + \text{Cs}^+$ calcd for $\text{C}_{16}\text{H}_{29}\text{NO}_2\text{SSi}$ 460.0743.

Iodide 27. Iodination of Alcohol 26. A solution of alcohol 26 (14.0 g, 42.7 mmol) in ether: MeCN (3:1, 250 mL) was cooled to 0°C . Imidazole (8.7 g, 128.1 mmol, 3.0 equiv), Ph_3P (16.8 g, 64.1 mmol, 1.5 equiv), and iodine (16.3 g, 64.1 mmol, 1.5 equiv) were sequentially added, and the mixture was stirred for 0.5 h at 0°C . A saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL) was added, followed by the addition of ether (600 mL). The organic phase was washed with brine (50 mL) and dried (MgSO_4), and the solvents were removed under

vacuum. Flash column chromatography (silica gel, 15% ether in hexanes) gave pure iodide 27 (16.6 g, 89%) as a colorless oil: R_f = 0.40 (silica gel, 10% ether in hexanes); $[\alpha]_D^{25}$ +11.0 (c 1.0, CHCl_3); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.90 (s, 1 H, $\text{SCH}=\text{C}$), 6.53 (s, 1 H, $\text{CH}=\text{CCH}_3$), 4.19 (dd, J = 7.7, 4.5 Hz, 1 H, CHOSi), 3.18 (t, J = 7.3 Hz, 2 H, CH_2I), 2.67 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 2.10–2.05 (m, 1 H, $\text{CH}_2\text{CH}_2\text{I}$), 2.01–1.95 (m, 1 H, $\text{CH}_2\text{CH}_2\text{I}$), 1.99 (s, 3 H, $\text{CH}=\text{CCH}_3$), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.00 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 164.4, 152.7, 140.9, 119.3, 115.4, 78.0, 40.2, 25.8, 19.2, 18.1, 13.9, 3.1, –4.6, –5.0; FAB HRMS (NBA) m/e 438.0768, $M + \text{H}^+$ calcd for $\text{C}_{16}\text{H}_{28}\text{INOSSi}$ 438.0784.

Phosphonium Salt 12. A mixture of iodide 27 (16.5 g, 37.7 mmol) and Ph_3P (10.9 g, 41.5 mmol, 1.1 equiv) was heated neat at 100 °C for 2 h. Purification by flash column chromatography (silica gel, CH_2Cl_2 ; then 7% MeOH in CH_2Cl_2) provided phosphonium salt 12 (25.9 g, 98%) as a white solid: R_f = 0.50 (silica gel, 7% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$ +3.7 (c 0.7, CHCl_3); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.78–7.28 (m, 15 H, aromatic), 6.97 (s, 1 H, $\text{SCH}=\text{C}$), 6.57 (s, 1 H, $\text{CH}=\text{CCH}_3$), 4.48 (dd, J = 6.3, 4.8 Hz, 1 H, CHOSi), 3.72–3.65 (m, 1 H, CH_2P), 3.31–3.25 (m, 1 H, CH_2P), 2.61 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 1.91 (s, 3 H, $\text{CH}=\text{CCH}_3$), 1.95–1.86 (m, 1 H, $\text{CH}_2\text{CH}_2\text{P}$), 1.82–1.74 (m, 1 H, $\text{CH}_2\text{CH}_2\text{P}$), 0.83 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.07 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), –0.02 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 164.4, 152.3, 139.4, 135.1, 133.3, 133.2, 130.5, 130.4, 128.1, 119.8, 117.9, 117.3, 116.5, 76.0, 28.9, 25.7, 19.1, 18.4, 17.9, 14.5, –4.8.

Hydrazone 28. Alkylation of Hydrazone 13. Hydrazone 13¹⁵ (20.0 g, 117.0 mmol, 1.0 equiv), dissolved in THF (80 mL), was added to a freshly prepared solution of LDA [19.75 mL of diisopropylamine (141.0 mmol, 1.2 equiv) was added to a solution of 88.1 mL of 1.6 M solution of $n\text{-BuLi}$ in hexanes (141 mmol, 1.2 equiv) in 160 mL of THF at 0 °C] at 0 °C. After the mixture was stirred at this temperature for 8 h, the resulting yellow solution was cooled to –100 °C and a solution of 4-iodo-1-(benzyloxy)butane (36.0 g, 124.0 mmol, 1.2 equiv) in THF (40 mL) was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature over 8 h and was then poured into saturated aqueous NH_4Cl solution (40 mL) and extracted with ether (3 \times 200 mL). The combined organic extracts were dried (MgSO_4), filtered, and evaporated. Purification by flash column chromatography on silica gel (20% ether in hexanes) provided hydrazone 28 as a yellow oil (35.8 g, 92%, de > 98% by ^1H NMR): R_f = 0.45 (silica gel, 50% ether in hexanes); $[\alpha]_D^{25}$ –55.0 (c 1.2, CHCl_3); IR (thin film) ν_{max} 2929, 2862, 1603, 1455, 1362, 1198, 1108, 737, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.33 (s, 5 H, Ph), 6.48 (d, J = 6.5 Hz, 1 H, $\text{CH}=\text{NN}$), 4.46 (s, 2 H, CH_2Ph), 3.54 (dd, J = 9.0, 3.8 Hz, 1 H, CH_2OCH_3), 3.44 (t, J = 6.5 Hz, 2 H, CH_2OBn), 3.40 (dd, J = 9.0, 6.8 Hz, 1 H, CH_2OCH_3), 3.33 (s, 3 H, OCH_3), 2.65 (m, 1 H, $\text{CHCH}_2\text{OCH}_3$), 2.29 (m, 1 H, $\text{CH}(\text{CH}_3)\text{C}=\text{N}$), 1.94–1.76 (m, 4 H), 1.61 (m, 2 H), 1.45–1.36 (m, 6 H), 1.01 (d, J = 6.8 Hz, 3 H, CHCH_3); ^{13}C NMR (125.7 MHz, CDCl_3) δ 144.6, 138.6, 128.2, 127.5, 127.3, 74.7, 72.7, 70.2, 63.4, 59.1, 50.4, 37.0, 35.2, 29.7, 26.4, 23.7, 22.0, 18.9; FAB HRMS (NBA) m/e 333.2552, $M + \text{H}^+$ calcd for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_2$ 333.2542.

Aldehyde 29. Cleavage of Hydrazone 28. Procedure A: A solution of hydrazone 28 (13.0 g, 39.1 mmol) in CH_2Cl_2 (50 mL) was treated with ozone at –78 °C until the solution turned blue-green. The solution was purged with oxygen for 2 min at –78 °C, allowed to warm to room temperature, and then concentrated. The crude mixture so obtained was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give aldehyde 29 (6.6 g, 77%) as a colorless oil. Procedure B: A solution of hydrazone 28 (30 g, 90.3 mmol) in MeI (100 mL) was heated at 60 °C. After 5 h, the reaction was complete (TLC) and the mixture was concentrated. The resulting crude product was suspended in n -pentane (360 mL) and was treated with 3 N aqueous HCl (360 mL). The two-phase system was vigorously stirred for 1 h, and the aqueous phase was extracted with n -pentane (3 \times 200 mL). The combined organic solution was dried (MgSO_4), concentrated, and purified by flash column chromatography (silica gel, 10% ether in hexanes) to give 29 (17.1 g, 86%): R_f = 0.49 (silica gel, 50% ether in hexanes); $[\alpha]_D^{25}$ +11.6 (c 1.7, CHCl_3); IR (thin film) ν_{max} 2932, 2856, 1715, 1450, 1361, 1272, 1202, 1102, 920, 732, 697 cm^{-1} ; ^1H NMR

(500 MHz, CDCl_3) δ 9.60 (d, J = 2.0 Hz, 1 H, CHO), 7.34 (s, 5 H, Ph), 4.50 (s, 2 H, CH_2Ph), 3.47 (t, J = 6.5 Hz, 2 H, CH_2OBn), 2.33 (m, 1 H, $\text{CH}(\text{CH}_3)\text{CO}$), 1.75–1.69 (m, 1 H), 1.65–1.61 (m, 2 H), 1.49–1.34 (m, 3 H), 1.08 (d, J = 7.0 Hz, 3 H, CHCH_3); ^{13}C NMR (125.7 MHz, CDCl_3) δ 205.0, 138.4, 128.2, 127.5, 127.4, 72.8, 69.9, 46.1, 30.1, 29.6, 23.6, 13.2; FAB HRMS (NBA) m/e 221.1538, $M + \text{H}^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$ 221.1542.

Alcohol 30. Reduction of Aldehyde 29. A solution of aldehyde 29 (17.0 g, 77.0 mmol) in MeOH (200 mL) was treated with NaBH_4 (8.6 g, 228 mmol, 3.0 equiv) at 0 °C for 15 min. The solution was then diluted with ether (400 mL), and saturated aqueous NH_4Cl solution (50 mL) was carefully added. The organic phase was washed with brine (50 mL), dried (MgSO_4), and concentrated. The crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol 30 (16.8 g, 98%) as a colorless oil: R_f = 0.23 (silica gel, 50% ether in hexanes); $[\alpha]_D^{25}$ –5.1 (c 1.9, CHCl_3); IR (thin film) ν_{max} 3401, 2931, 2860, 1455, 1361, 1267, 1202, 1102, 1037, 937, 732, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.50 (dd, J = 11.0, 6.0 Hz, 1 H, CH_2OH), 3.48 (t, J = 6.5 Hz, 2 H, CH_2OBn), 3.42 (dd, J = 11.0, 6.5 Hz, 1 H, CH_2OH), 1.65–1.59 (m, 2 H), 1.47–1.34 (m, 4 H), 1.15–1.12 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H, CHCH_3); ^{13}C NMR (125.7 MHz, CDCl_3) δ 138.6, 128.2, 127.6, 127.3, 72.9, 70.3, 68.1, 35.7, 32.9, 30.1, 23.6, 14.1; FAB HRMS (NBA) m/e 223.1705, $M + \text{H}^+$ calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2$ 223.1698.

Silyl Ether 31. Silylation of Alcohol 30. Alcohol 30 (17.0 g, 76.0 mmol) was dissolved in CH_2Cl_2 (350 mL), the solution was cooled to 0 °C and Et_3N (21.2 mL, 152.0 mmol, 2.0 equiv) and 4-DMAP (185 mg, 1.52 mmol, 0.05 equiv) were added. After the mixture was stirred for 5 min, *tert*-butyldimethylsilyl chloride (17.3 g, 115 mmol, 1.5 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 2 h and then at 25 °C for 10 h. Methanol (20 mL) was added at 0 °C, and the solvents were removed under reduced pressure. Ether (200 mL) and saturated aqueous NH_4Cl solution (30 mL) were sequentially added, and the organic phase was separated. The aqueous phase was extracted with ether (2 \times 100 mL), and the combined organic layer was dried (MgSO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure silyl ether 31 (24.4 g, 95%): R_f = 0.54 (silica gel, 10% ether in hexanes); $[\alpha]_D^{25}$ –2.3 (c 1.1, CHCl_3); IR (thin film) ν_{max} 2931, 2860, 1461, 1361, 1249, 1091, 839, 773, 738 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.48 (t, J = 6.5 Hz, 2 H, CH_2OBn), 3.43 (dd, J = 10.5, 6.0 Hz, 1 H, CH_2OSi), 3.36 (dd, J = 10.5, 6.5 Hz, 1 H, CH_2OSi), 1.64–1.60 (m, 3 H), 1.47–1.29 (m, 3 H), 1.15–1.05 (m, 1 H), 0.90 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.87 (d, J = 6.8 Hz, 3 H, CHCH_3), 0.043 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.041 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 138.6, 128.2, 127.5, 127.3, 72.7, 70.3, 68.3, 35.6, 32.9, 30.0, 25.8, 23.5, 18.1, 16.6, –5.5; FAB HRMS (NBA) m/e 337.2553, $M + \text{H}^+$ calcd for $\text{C}_{20}\text{H}_{36}\text{O}_2\text{Si}$ 337.2563.

Alcohol 32. Hydrogenolysis of Benzyl Ether 31. To a solution of benzyl ether 31 (21.0 g, 62.5 mmol) in THF (200 mL) was added 10% $\text{Pd}(\text{OH})_2/\text{C}$ (1.0 g). The reaction was allowed to proceed under an atmosphere of H_2 at a pressure of 50 psi and at 25 °C (Parr hydrogenator apparatus). After 15 min, no starting benzyl ether was detected by TLC and the mixture was filtered through Celite. The clear solution was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol 32 (14.7 g, 95%) as a colorless oil: R_f = 0.32 (silica gel, 50% ether in hexanes); $[\alpha]_D^{25}$ –3.6 (c 3.6, CHCl_3); IR (thin film) ν_{max} 3342, 2931, 2860, 1467, 1384, 1249, 1085, 838, 773, 667 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.63 (t, J = 7.0 Hz, 2 H, CH_2OH), 3.42 (dd, J = 11.0, 6.0 Hz, 1 H, CH_2OSi), 3.35 (dd, J = 11.0, 7.0 Hz, 1 H, CH_2OSi), 1.57–1.53 (m, 3 H), 1.42–1.39 (m, 3 H), 1.16–1.06 (m, 1 H), 0.88 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.85 (d, J = 6.5 Hz, 3 H, CHCH_3), 0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.02 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 68.2, 62.7, 35.6, 32.9, 32.8, 25.7, 23.0, 18.2, 16.5, –5.5; FAB HRMS (NBA) m/e 247.2097, $M + \text{H}^+$ calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2\text{Si}$ 247.2093.

Aldehyde 10. Oxidation of Alcohol 32. To a solution of oxalyl chloride (5.6 mL, 65.0 mmol, 2.0 equiv) in CH_2Cl_2 (250 mL) was added dropwise DMSO (9.2 mL, 130 mmol, 4.0 equiv) at –78 °C. After the mixture was stirred for 15 min, a solution of alcohol 32 (8.0 g, 32.0

mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise at -78°C over a 15 min period. The solution was stirred for a further 30 min at -78°C , and Et_3N (27.1 mL, 194 mmol, 6.0 equiv) was added at the same temperature. The reaction mixture was allowed to warm to 0°C over 30 min, and then ether (400 mL) was added, followed by saturated aqueous NH_4Cl solution (100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2×300 mL). The combined organic solution was dried (MgSO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde **10** (7.9 g, 98%) as a colorless oil: $R_f = 0.64$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{25} -5.1$ (c 0.7, CHCl_3); IR (thin film) ν_{max} 2952, 2858, 1728, 1466, 1389, 1254, 1095, 841, 776 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.74 (t, $J = 1.5$ Hz, 1 H, CHO), 3.39 (dd, $J = 9.8, 6.1$ Hz, 1 H, CH_2OSi), 3.36 (dd, $J = 9.8, 6.3$ Hz, 1 H, CH_2OSi), 2.39 (m, 2 H, CH_2CHO), 1.71–1.64 (m, 1 H), 1.61–1.53 (m, 2 H), 1.44–1.38 (m, 1 H), 1.11–1.05 (m, 1 H), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.85 (d, $J = 6.5$ Hz, 3 H, CHCH_3), 0.019 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.004 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 202.7, 68.9, 44.1, 35.5, 32.6, 25.8, 23.0, 18.2, 16.5, –5.5; FAB HRMS (NBA) m/e 245.1932, $M + \text{H}^+$ calcd for $\text{C}_{13}\text{H}_{24}\text{O}_2\text{Si}$ 245.1937.

Alcohol 33. To a cold (0°C) solution of aldehyde **10** (7.8 g, 32.0 mmol) in THF (300 mL) was slowly added MeMgBr (1.0 M solution in THF, 48.0 mL, 48.0 mmol, 1.5 equiv). The reaction mixture was stirred for 15 min at 0°C , and then it was diluted with ether (500 mL) and quenched by careful addition of saturated aqueous NH_4Cl solution (100 mL). The organic phase was washed with brine (100 mL), dried (MgSO_4), and concentrated. The crude product so obtained was purified by flash column chromatography (silica gel, 30% ether in hexanes) to give alcohol **33** (7.0 g, 84%) as a colorless oil: $R_f = 0.38$ (silica gel, 50% ether in hexanes); IR (thin film) ν_{max} 3352, 2931, 2858, 1465, 1384, 1253, 1096, 839, 775 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.79 (m, 1 H, $\text{CH}(\text{CH}_3)\text{OH}$), 3.43 (dd, $J = 9.8, 6.0$ Hz, 1 H, CH_2OSi), 3.36 (dd, $J = 9.8, 6.8$ Hz, 1 H, CH_2OSi), 1.61–1.57 (m, 1 H), 1.47–1.35 (m, 4 H), 1.30–1.26 (m, 1 H), 1.19 (d, $J = 6.1$ Hz, 3 H, $\text{CH}(\text{OH})\text{CH}_3$), 1.09–1.05 (m, 1 H), 0.89 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.86 (d, $J = 6.7$ Hz, 3 H, CHCH_3), 0.04 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 68.2, 67.9, 39.5, 35.6, 33.0, 25.9, 23.4, 23.1, 18.2, 16.6, –5.4; AB HRMS (NBA) m/e 261.2256, $M + \text{H}^+$ calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{Si}$ 261.2250.

Ketone 11. Oxidation of Alcohol 33. To a solution of alcohol **33** (7.0 g, 27.0 mmol) in CH_2Cl_2 (250 mL) were added molecular sieves (4 Å, 6.0 g), 4-methylmorpholine *N*-oxide (NMO) (4.73 g, 40.0 mmol, 1.5 equiv), and tetrapropylammonium perruthenate (TPAP) (189 mg, 54 mmol, 0.02 equiv) at room temperature. After being stirred for 5 min (depletion of starting material, TLC), the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% ether in hexanes) to give ketone **11** (6.6 g, 50%) as a colorless oil: $R_f = 0.67$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{25} -4.5$ (c 1.1, CHCl_3); IR (thin film) ν_{max} 2931, 2849, 1713, 1461, 1355, 1249, 1161, 1091, 838, 773, 667 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.41 (dd, $J = 9.8, 6.0$ Hz, 1 H, CH_2OSi), 3.36 (dd, $J = 9.8, 3$ Hz, 1 H, CH_2OSi), 2.41 (m, 2 H, CH_2COCH_3), 2.13 (s, 3 H, OCH_3), 1.68–1.48 (m, 3 H), 1.42–1.35 (m, 1 H), 1.09–1.00 (m, 1 H), 0.88 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.86 (d, $J = 6.7$ Hz, 3 H, CHCH_3), 0.03 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 209.8, 68.0, 43.9, 35.5, 32.6, 29.7, 25.8, 21.2, 18.2, 16.4, –5.5; FAB HRMS (NBA) m/e 209.097, $M + \text{H}^+$ calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{Si}$ 259.2093.

Iodide 46. Iodination of Alcohol 32. A solution of alcohol **32** (8 g, 15.0 mmol) in ether:MeCN, 3:1 (150 mL), was cooled to 0°C . Iodazole (3.1 g, 45.0 mmol, 3.0 equiv), Ph_3P (5.9 g, 22.5 mmol, 1.5 equiv), and iodine (5.7 g, 22.5 mmol, 1.5 equiv) were sequentially added, and the reaction mixture was stirred at 0°C for 0.5 h. A saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (200 mL) was added followed by ether (200 mL). The organic phase was washed with brine (200 mL) and dried (MgSO_4), and the solvents were removed under vacuum. The crude product was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give pure iodide **46** (4.9 g, 91%) as a colorless oil: $R_f = 0.68$ (silica gel, 10% ether in hexanes); $[\alpha]_D^{25} -4.3$ (c 1.2, CHCl_3); IR (thin film) ν_{max} 2929, 2860, 1461, 1386, 1248, 1090, 577, 664 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.42 (dd, $J = 0, 6.5$ Hz, 1 H, CH_2OSi), 3.38 (dd, $J = 10.0, 6.0$ Hz, 1 H, CH_2

OSi), 3.19 (t, $J = 7.0$ Hz, 2 H, CH_2I), 1.85–1.78 (m, 2 H), 1.61–1.55 (m, 1 H), 1.47–1.33 (m, 3 H), 1.10–1.02 (m, 1 H, CH_2), 0.89 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.87 (d, $J = 6.7$ Hz, 3 H, CHCH_3), 0.04 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 68.1, 35.4, 33.7, 31.8, 27.8, 25.8, 18.2, 16.5, 7.1, –5.5; FAB HRMS (NBA) m/e 229.1983, $M - \text{I}^-$ calcd for $\text{C}_{13}\text{H}_{23}\text{IOSi}$ 229.1988.

Phosphonium Salt 47. A mixture of iodide **46** (4.7 g, 13.1 mmol) and Ph_3P (3.8 g, 14.4 mmol, 1.1 equiv) was heated neat at 100°C for 2 h. Purification by flash column chromatography (silica gel, CH_2Cl_2 – 7% MeOH in CH_2Cl_2) provided phosphonium salt **47** (7.4 g, 91%) as a white solid: $R_f = 0.42$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -7.3$ (c 1.5, CHCl_3); IR (thin film) ν_{max} 2931, 2849, 1578, 1461, 1431, 1243, 1184, 1102, 997, 914, 838, 720, 685, 532, 503 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.82–7.77 (m, 9 H, Ph), 7.74–7.68 (m, 6 H, Ph), 3.62 (dt, $J = 12.5, 8.0$ Hz, 2 H, CH_2P), 3.34 (dd, $J = 9.5, 6.5$ Hz, 1 H, CH_2OSi), 3.30 (dd, $J = 9.5, 6.5$ Hz, 1 H, CH_2OSi), 1.69–1.55 (m, 4 H), 1.50–1.46 (m, 1 H), 1.39–1.32 (m, 1 H), 1.10–1.01 (m, 1 H), 0.83 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.79 (d, $J = 6.6$ Hz, 3 H, CHCH_3), –0.04 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 135.0, 133.6, 133.5, 133.2, 130.5, 130.4, 68.0, 35.2, 32.4, 27.8, 25.8, 23.2, 22.7, 18.2, 16.4, –5.5.

Olefin 34. Method A. From Phosphonium Salt 12 and Aldehyde 10: Phosphonium salt **12** (13.60 g, 19.4 mmol, 1.2 equiv) was dissolved in THF (80 mL, 0.2 M), and the solution was cooled to 0°C . Sodium hexamethyldisilylamide (NaHMDS, 19.4 mL, 19.4 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added, and the resulting mixture was stirred for 15 min before aldehyde **10** (3.96 g, 16.2 mmol, 1.0 equiv, in 10 mL of THF) was added at the same temperature. Stirring was continued for another 15 min at 0°C , and then the reaction mixture was quenched with saturated aqueous NH_4Cl solution (25 mL). Ether (250 mL) was added, and the organic phase was separated and washed with brine (2×40 mL), dried (MgSO_4), and concentrated under *vacuo*. The crude product was purified by flash column chromatography (silica gel, 10% ether in hexane) to afford olefin **34** (6.70 g, 77%) as a mixture of *Z*- and *E*-isomers (ca. 9:1 by ^1H NMR). **Method B. From Phosphonium Salt 47 and Aldehyde 15:** Phosphonium salt **47** (7.40 g, 11.96 mmol, 1.2 equiv) was dissolved in THF (120 mL, 0.1 M), and the solution was cooled to 0°C . Sodium hexamethyldisilylamide (NaHMDS, 11.96 mL, 11.96 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added at the same temperature, and the resulting mixture was stirred for 15 min, before aldehyde **15** (3.20 g, 9.83 mmol, 1.0 equiv, in 20 mL of THF) was slowly added. Stirring was continued for another 15 min at 0°C , and then the mixture was quenched with saturated aqueous NH_4Cl solution (150 mL). Ether (200 mL) was added, and the organic phase was separated and washed with brine (2×150 mL), dried (MgSO_4), and concentrated under reduced pressure to afford the crude product. Flash column chromatography (silica gel, 10% ether in hexane) furnished olefin **34** (3.65 g, 69% yield) as a mixture of *Z*- and *E*-isomers (ca. 9:1 by ^1H NMR): $R_f = 0.75$ (silica gel, 50% ether in hexane); $[\alpha]_D^{25} +4.0$ (c 0.5, CHCl_3); IR (thin film) ν_{max} 2930, 2856, 1465, 1388, 1253, 1089, 939, 838 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) (signals for the *Z*-isomer (**34**) only reported) δ 6.92 (s, 1 H, $\text{SCH}=\text{C}$), 6.46 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.49–5.31 (m, 2 H, $\text{CH}=\text{CH}$), 4.12 (dd, $J = 6.5, 6.4$ Hz, 1 H, CHOSi), 3.44 (dd, $J = 9.8, 5.8$ Hz, 1 H, CH_2OSi), 3.34 (dd, $J = 9.8, 6.8$ Hz, 1 H, CH_2OSi), 2.71 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 2.39–2.24 (m, 2 H, CH_2CHOSi), 2.00 (s, 3 H, $\text{CH}=\text{CCH}_3$), 2.05–1.96 (m, 2 H), 1.59–1.51 (m, 1 H), 1.42–1.23 (m, 3 H), 1.10–0.98 (m, 1 H), 0.89 (s, 18 H, $\text{Si}(\text{CH}_3)_3$), 0.85 (d, $J = 6.8$ Hz, 3 H, CH_3CH), 0.06 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 6 H, $\text{Si}(\text{CH}_3)_2$), 0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 164.3, 153.1, 142.2, 131.4, 125.7, 118.8, 114.9, 78.7, 68.3, 35.7, 34.6, 32.9, 27.8, 27.1, 25.9, 25.8, 19.2, 18.3, 18.2, 16.7, 13.9, –4.7, –4.9, –5.4; FAB HRMS (NBA) m/e 538.3582, $M + \text{H}^+$ calcd for $\text{C}_{27}\text{H}_{53}\text{NO}_2\text{SSi}_2$ 538.3570.

Alcohol 35. Compound **34** (1.77 g, 3.29 mmol) was dissolved in CH_2Cl_2 :MeOH (1:1, 66 mL), the solution was cooled to 0°C , and CSA (764 mg, 3.29 mmol, 1.0 equiv) was added over a 5 min period. The mixture was stirred for 30 min at 0°C and then for 1 h at 25°C . Et_3N (2.0 mL) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished the desired alcohol **35** (1.2 g, 86%); $R_f = 0.72$ (silica gel, 80% ether in hexanes); $[\alpha]_D^{25} +1.1$ (c 1.0, CHCl_3); IR (thin film) ν_{max} 3370, 2923, 2857, 1464, 1384, 1253, 1185, 1074, 836, 776

cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.91 (s, 1 H, $\text{SCH}=\text{C}$), 6.44 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.45–5.32 (m, 2 H, $\text{CH}=\text{CH}$), 4.12 (dd, $J = 6.5$, 6.4 Hz, 1 H, CHOSi), 3.46 (dd, $J = 10.5$, 5.9 Hz, 1 H, CH_2OH), 3.37 (dd, $J = 10.5$, 6.5 Hz, 1 H, CH_2OH), 2.68 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 2.39–2.21 (m, 2 H, CH_2CHOSi), 2.21 (s, 1 H, OH), 1.98 (s, 3 H, $\text{CH}=\text{CCH}_3$), 2.05–1.95 (m, 2 H), 1.59–1.51 (m, 1 H), 1.42–1.23 (m, 3 H), 1.10–0.98 (m, 1 H), 0.88 (d, $J = 6.5$ Hz, 3 H, CH_3CH), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), –0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 164.4, 152.9, 142.2, 131.2, 125.8, 118.7, 114.8, 78.6, 67.9, 35.5, 34.6, 32.7, 27.5, 26.9, 25.8, 25.7, 18.9, 16.5, 13.7, –4.8, –5.1; FAB HRMS (NBA/NaI) m/e 446.2534, $M + \text{Na}^+$ calcd for $\text{C}_{23}\text{H}_{31}\text{NO}_2\text{SSi}$ 446.2525.

Aldehyde 7. Oxidation of Alcohol 35. Alcohol 35 (1.9 g, 4.5 mmol) was dissolved in CH_2Cl_2 (45 mL, 0.1 M). DMSO (13.5 mL), Et_3N (3.0 mL, 22.4 mmol, 5.0 equiv), and $\text{SO}_3\cdot\text{pyr}$ (1.43 g, 8.98 mmol, 2.0 equiv) were added at 25 °C, and the resulting mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (100 mL) and ether (200 mL) were added sequentially. The organic phase was washed with brine (2 \times 30 mL) and dried (MgSO_4), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 30% ether in hexanes) furnished aldehyde 7 (1.79 g, 94%); $R_f = 0.55$ (silica gel, 40% ether in hexanes); $[\alpha]_D^{25} + 13.3$ (c 0.7, CHCl_3); IR (thin film) ν_{max} 2930, 2856, 1725, 1504, 1462, 1385, 1253, 1182, 1076, 938, 836, 776 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 9.57 (d, $J = 1.8$ Hz, 1 H, CHO), 6.91 (s, 1 H, $\text{SCH}=\text{C}$), 6.44 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.45–5.35 (m, 2 H, $\text{CH}=\text{CH}$), 4.11 (dd, $J = 6.6$, 6.3 Hz, 1 H, CHOSi), 2.69 (s, 3 H, $\text{N}=\text{C}(\text{S})\text{CH}_3$), 2.34–2.24 (m, 3 H), 2.05–2.01 (m, 2 H), 1.98 (s, 3 H, $\text{CH}=\text{CCH}_3$), 1.71–1.64 (m, 1 H), 1.41–1.29 (m, 3 H), 1.05 (d, $J = 7.0$ Hz, 3 H, CH_3CH), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), –0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 205.2, 164.4, 153.0, 142.0, 130.6, 126.4, 118.8, 115.0, 78.7, 46.2, 34.7, 30.0, 27.3, 26.9, 25.8, 19.2, 18.2, 13.9, 13.2, –4.7, –5.0; FAB HRMS (NBA) m/e 422.2559, $M + \text{H}^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_2\text{SSi}$ 422.2549.

Aldol Reaction of Keto Acid 9 with Aldehyde 7. A solution of keto acid 9 (1.52 g, 5.10 mmol, 1.2 equiv) in THF (10 mL) was added dropwise to a freshly prepared solution of LDA (diisopropylamine (1.78 mL, 12.78 mmol) was added to *n*-BuLi (7.95 mL, 1.6 M solution in hexanes, 12.78 mmol) in 20 mL of THF at 0 °C) at –78 °C. After being stirred for 15 min, the solution was allowed to warm to –40 °C, and after 0.5 h at that temperature, it was recooled to –78 °C. A solution of aldehyde 7 (1.79 g, 4.24 mmol, 1.0 equiv) was added dropwise, and the resulting mixture was stirred for 15 min and then quenched at –78 °C by slow addition of saturated aqueous NH_4Cl solution (20 mL). The reaction mixture was warmed to 0 °C, and AcOH (2.03 mL, 26.84 mmol, 6.3 equiv) was added, followed by addition of EtOAc (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 \times 25 mL). The combined organic solution was dried over MgSO_4 and concentrated under vacuum to afford a mixture of aldol products **36a**–**36b** in a ca. 1:1 ratio (^1H NMR) and unreacted keto acid 9. The mixture was dissolved in CH_2Cl_2 (50 mL) and treated, at 0 °C, with 2,6-lutidine (3.2 mL, 27.36 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.2 mL, 18.24 mmol). After stirring for 2 h (complete reaction by TLC), aqueous HCl (20 mL, 10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (3 \times 20 mL), and the combined organic solution was washed with brine (50 mL), dried (MgSO_4), and concentrated under reduced pressure to give a mixture of the *tert*-*tert*-butyldimethylsilyl ethers **37a**, **b**. The crude product was dissolved in MeOH (50 mL), and K_2CO_3 (1.40 g, 10.20 mmol) was added at 25 °C. The reaction mixture was vigorously stirred for 15 min and then filtered. The residue was washed with MeOH (20 mL), and the solution was acidified with ion-exchange resin (DOWEX 50WX8–200) to pH 4–5 and filtered again. The solvent was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with EtOAc (4 \times 25 mL), and the combined organic solution was dried (MgSO_4), filtered, and concentrated to furnish a mixture of carboxylic acids **38**, **39**, and **9**. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure acids **38** (1.1 g, 31% from **7**) and **39** (1.0 g, 30% from **7**) as colorless oils. **38**: $R_f = 0.61$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} - 8.8$ (c 0.8, CHCl_3); IR (thin film)

ν_{max} 2931, 2856, 1712, 1466, 1254, 1083, 836 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.94 (s, 1 H, $\text{SCH}=\text{C}$), 6.61 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.44–5.41 (m, 2 H, $\text{CH}=\text{CH}$), 4.40 (dd, $J = 6.5$, 3.2 Hz, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 4.11 (dd, $J = 6.5$, 5.9 Hz, 1 H, CH_2CHOSi), 3.75 (dd, $J = 6.5$, 3.0 Hz, 1 H, $\text{CH}(\text{CH}_3)\text{CHOSi}$), 3.12 (dq, $J = 7.0$, 6.5 Hz, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.69 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.48 (dd, $J = 16.0$, 3.2 Hz, 1 H, CH_2COOH), 2.35 (dd, $J = 16.0$, 6.7 Hz, 1 H, CH_2COOH), 2.39–2.28 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}$), 2.10–1.92 (m, 2 H, $\text{CH}=\text{CHCH}_2$), 1.95 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.42–1.30 (m, 5 H, $\text{CH}(\text{CH}_3)$, 2 \times CH_2), 1.18 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.10 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.06 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.90–0.85 (m, 30 H, $\text{CH}(\text{CH}_3)$, 3 \times $\text{Si}(\text{CH}_3)_2$), 0.12 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.07 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 218.1, 176.7, 164.8, 152.8, 142.6, 131.3, 125.9, 118.6, 114.7, 78.6, 77.4, 73.4, 53.5, 44.9, 40.1, 38.8, 34.6, 30.7, 28.0, 27.8, 26.2, 26.0, 25.8, 23.6, 19.1, 18.8, 18.5, 18.2, 17.4, 15.7, 13.8, –3.7, –3.8, –4.2, –4.6, –4.7, –4.9; FAB HRMS (NBA/CsI) m/e 970.4318, $M + \text{Cs}^+$ calcd for $\text{C}_{44}\text{H}_{63}\text{NO}_6\text{SSi}_3$ 970.4303. **39**: $R_f = 0.70$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} + 2.2$ (c 3.5, CHCl_3); IR (thin film) ν_{max} 2929, 2856, 1713, 1470, 1386, 1254, 1082, 988, 836, 776 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.91 (s, 1 H, $\text{SCH}=\text{C}$), 6.45 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.44–5.38 (m, 1 H, $\text{CH}=\text{CH}$), 5.37–5.32 (m, 1 H, $\text{CH}=\text{CH}$), 4.55 (dd, $J = 6.7$, 3.7 Hz, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 4.11 (dd, $J = 6.7$, 6.2 Hz, 1 H, CH_2CHOSi), 3.83 (d, $J = 8.4$, 1 H, $\text{CH}(\text{CH}_3)\text{CHOSi}$), 3.09 (dq, $J = 7.0$, 6.9 Hz, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.73 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.40 (dd, $J = 16.3$, 3.8 Hz, 1 H, CH_2COOH), 2.35–2.22 (m, 3 H, CH_2COOH , $\text{CH}_2\text{CH}=\text{CH}$), 1.98–1.94 (m, 2 H, $\text{CH}=\text{CHCH}_2$), 1.92 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.34–1.21 (m, 5 H, $\text{CH}(\text{CH}_3)$, 2 \times CH_2), 1.18 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.07 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.05 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.89 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.88 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.85 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.82 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.07 (s, 6 H, 2 \times $\text{Si}(\text{CH}_3)_2$), 0.06 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 217.7, 175.3, 165.4, 152.4, 143.1, 131.3, 125.9, 118.3, 114.6, 78.6, 76.7, 72.3, 53.8, 45.7, 40.1, 37.9, 34.9, 34.6, 27.7, 27.3, 26.3, 26.2, 26.0, 25.8, 22.4, 19.0, 18.6, 18.2, 18.1, 16.8, 13.9, 13.5, –3.4, –3.6, –4.3, –4.6, –4.7, –4.9; FAB HRMS (NBA/CsI) m/e 970.4331, $M + \text{Cs}^+$ calcd for $\text{C}_{44}\text{H}_{63}\text{NO}_6\text{SSi}_3$ 970.4303.

Hydroxy Acid 5. Selective Desilylation of Tris(silyl ether) 38. A solution of tris(silyl ether) **38** (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After being stirred for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 \times 10 mL), and the combined organic phase was washed with brine (10 mL), dried (MgSO_4), and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide hydroxy acid **5** (203 mg, 78%) as a yellow oil: $R_f = 0.40$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} - 19.2$ (c 0.1, CHCl_3); IR (thin film) ν_{max} 3358, 2932, 2857, 1701, 1466, 1254, 1088, 988, 835 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.95 (s, 1 H, $\text{SCH}=\text{C}$), 6.67 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.58–5.54 (m, 1 H, $\text{CH}=\text{CH}$), 5.43–5.39 (m, 1 H, $\text{CH}=\text{CH}$), 4.39 (dd, $J = 6.7$, 3.9 Hz, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 4.18 (dd, $J = 7.5$, 5.0 Hz, 1 H, CH_2CHOH), 3.78 (dd, $J = 6.9$, 1.0 Hz, 1 H, $\text{CH}(\text{CH}_3)\text{CHOSi}$), 3.11 (dq, $J = 6.9$, 6.7 Hz, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.70 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.43 (dd, $J = 16.2$, 3.9 Hz, 1 H, CH_2COOH), 2.40–2.35 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}$), 2.35 (dd, $J = 16.2$, 6.7 Hz, 1 H, CH_2COOH), 2.15–2.10 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 2.00 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.99–1.95 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 1.48–1.30 (m, 5 H, $\text{CH}(\text{CH}_3)$, 2 \times CH_2), 1.18 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.08 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.05 (d, $J = 6.7$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.89–0.84 (m, 21 H, $\text{CH}(\text{CH}_3)$, $\text{Si}(\text{CH}_3)_2$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 218.9, 175.4, 166.3, 152.8, 143.5, 134.4, 125.7, 119.5, 115.9, 74.4, 54.7, 45.5, 40.9, 40.0, 34.3, 31.9, 30.6, 28.9, 28.8, 27.0, 26.8, 26.7, 24.4, 20.0, 19.6, 19.3, 19.1, 17.9, 17.1, 15.5, –2.9, –3.1, –3.3, –3.8; FAB HRMS (NBA/CsI) m/e 856.3459, $M + \text{Cs}^+$ calcd for $\text{C}_{38}\text{H}_{59}\text{NO}_6\text{SSi}_2$ 856.3439.

Hydroxy Acid 40. Selective Desilylation of Tris(silyl ether) 39. Carboxylic acid **39** (150 mg, 0.18 mmol) was converted to hydroxy acid **40** (107 mg, 82%) according to the procedure described above for **5**. **40**: yellow oil; $R_f = 0.45$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} - 8.0$ (c 0.2, CHCl_3); IR (thin film) ν_{max} 3225, 2943, 2860, 1719,

1690, 1461, 1384, 1296, 1250, 1190, 1085, 985, 832, 761, 667 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.93 (s, 1 H, $\text{SCH}=\text{C}$), 6.60 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.54–5.50 (m, 1 H, $\text{CH}=\text{CH}$), 5.40–5.34 (m, 1 H, $\text{CH}=\text{CH}$), 4.54 (dd, $J = 6.4, 3.7$ Hz, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 4.15 (dd, $J = 6.5, 6.3$ Hz, 1 H, CH_2CHOH), 3.82 (d, $J = 7.6$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.71 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.37–2.32 (m, 3 H, $\text{CH}_2\text{CH}=\text{CH}$, CH_2COOH), 2.30 (dd, $J = 16.3, 6.4$ Hz, 1 H, CH_2COOH), 2.15–2.10 (m, 2 H, $\text{CH}=\text{CHCH}_2$), 1.97 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.36–1.18 (m, 5 H, $\text{CH}(\text{CH}_3)$, 2 \times CH_2), 1.17 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.07 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.05 (d, $J = 6.8$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.88 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.85–0.82 (m, 12 H, $\text{CH}(\text{CH}_3)$, $\text{Si}(\text{CH}_3)_3$), 0.07 (s, 3 H, $\text{Si}(\text{CH}_3)_3$), 0.06 (s, 3 H, $\text{Si}(\text{CH}_3)_3$), 0.05 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 218.2, 175.4, 165.4, 152.2, 142.0, 133.1, 124.9, 118.6, 115.1, 74.4, 53.8, 45.8, 40.2, 38.9, 37.7, 34.8, 33.2, 27.9, 27.5, 27.1, 26.2, 26.1, 26.0, 22.6, 21.4, 18.8, 18.6, 16.9, 14.5, 13.3, –3.4, –3.6, –4.3, –4.6; FAB HRMS (NBA/CsI) m/e 856.3402, $\text{M} + \text{Cs}^+$ calcd for $\text{C}_{33}\text{H}_{47}\text{NO}_5\text{SSi}_2$ 856.3439.

Lactone 41. Macrolactonization of Hydroxy Acid 5. A solution of hydroxy acid 5 (200 mg, 0.28 mmol) in THF (4 mL) was treated at 0 $^\circ\text{C}$ with Et_3N (0.23 mL, 1.68 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.40 mmol, 5.0 equiv). The reaction mixture was stirred at 0 $^\circ\text{C}$ for 15 min and then added to a solution of 4-DMAP (342 mg, 2.80 mmol, 10.0 equiv) in toluene (140 mL) at 25 $^\circ\text{C}$ and stirred at that temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% ether in hexanes, and the resulting solution was concentrated. Purification by flash column chromatography (silica gel, 2% MeOH in CH_2Cl_2) furnished lactone 41 (178 mg, 90%) as a colorless oil: $R_f = 0.37$ (silica gel, 30% ether in hexanes); $[\alpha]_D^{25} -22.9$ (c 0.3, CHCl_3); IR (thin film) ν_{max} 2925, 2854, 1734, 1693, 1464, 1381, 1252, 1187, 1158, 1099, 988, 829, 758 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.98 (s, 1 H, $\text{SCH}=\text{C}$), 6.58 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.53 (m, 1 H, $\text{CH}=\text{CH}$), 5.43–5.34 (m, 1 H, $\text{CH}=\text{CH}$), 5.00 (d, $J = 10.2$ Hz, 1 H, $\text{O}=\text{COCH}$), 4.03 (d, $J = 10.5$ Hz, 1 H, CHOSi), 3.89 (d, $J = 9.0$ Hz, 1 H, CHOSi), 2.98 (dq, $J = 6.9, 6.7$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.85 (d, $J = 16.7$ Hz, 1 H, CH_2COO), 2.72 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.66 (dd, $J = 16.7, 10.7$ Hz, 1 H, CH_2COO), 2.40–2.30 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 2.11 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 2.10–2.04 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}$), 1.92–1.83 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 1.66–1.38 (m, 5 H, $\text{CH}(\text{CH}_3)$, 2 \times CH_2), 1.17 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.13 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.06 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.94 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.92 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.83 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.07 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), –0.12 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 215.0, 171.3, 165.4, 135.7, 135.1, 125.8, 122.7, 119.9, 115.9, 79.5, 76.4, 53.3, 48.0, 38.8, 31.7, 31.3, 29.7, 29.2, 28.4, 26.4, 26.2, 26.1, 25.9, 24.2, 19.1, 18.7, 18.6, 17.7, 15.3, –3.1, –3.2, –3.7, –5.8; FAB HRMS (NBA) m/e 706.4382, $\text{M} + \text{H}^+$ calcd for $\text{C}_{33}\text{H}_{47}\text{NO}_5\text{SSi}_2$ 706.4357.

Lactone 42. Macrolactonization of Hydroxy Acid 40. The cyclization of hydroxy acid 40 (100 mg, 0.14 mmol) was carried out exactly as described for 41 above and yielded lactone 42 (84 mg, 85%) as a colorless oil: $R_f = 0.40$ (silica gel, 30% ether in hexanes); $[\alpha]_D^{25} -40.5$ (c 0.2, CHCl_3); IR (thin film) ν_{max} 2929, 2855, 1739, 1690, 1469, 1384, 1253, 1180, 1089, 1053, 985, 835, 775 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.94 (s, 1 H, $\text{SCH}=\text{C}$), 6.53 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.55–5.46 (m, 1 H, $\text{CH}=\text{CH}$), 5.39–5.30 (m, 1 H, $\text{CH}=\text{CH}$), 5.32 (dd, $J = 7.0, 3.0$ Hz, 1 H, $\text{O}=\text{COCH}$), 4.43 (dd, $J = 7.5, 2.9$ Hz, 1 H, CHOSi), 3.99 (d, $J = 7.1$ Hz, 1 H, CHOSi), 3.20 (dq, $J = 7.3, 7.1$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.71 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.59 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 2.21 (dd, $J = 14.6, 3.2$ Hz, 1 H, CH_2COO), 2.20 (dd, $J = 14.6, 7.6$ Hz, 1 H, CH_2COO), 2.16 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 2.15–1.95 (m, 3 H, $\text{CH}=\text{CHCH}_2$, $\text{CH}_2\text{CH}=\text{CH}$), 1.60–1.50 (m, 3 H, $\text{CH}(\text{CH}_3)$, 2 \times CH_2), 1.47–1.35 (m, 2 H, $\text{CH}(\text{CH}_3)$, 2 \times CH_2), 1.24 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.11 (d, $J = 7.2$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.09 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 0.90 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.86 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.83 (d, $J = 6.7$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.09 (s, 6 H, 2 \times $\text{Si}(\text{CH}_3)_2$), 0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), –0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 221.2, 171.6, 165.8, 134.9, 134.1, 125.7, 125.2, 120.7, 117.1, 78.8, 75.2, 74.5, 54.3, 48.1, 42.5, 37.9, 33.7, 32.4, 26.8, 26.7, 26.5, 26.2,

25.8, 19.7, 19.2, 19.0, 18.8, 17.7, 15.9, 14.1, –3.0, –3.3, –3.7, –4.3; FAB HRMS (NBA) m/e 706.4333, $\text{M} + \text{H}^+$ calcd for $\text{C}_{33}\text{H}_{47}\text{NO}_5\text{SSi}_2$ 706.4357.

Dihydroxy Lactone 3. To lactone 41 (50 mg, 0.071 mmol), cooled to –20 $^\circ\text{C}$, was added a freshly prepared 20% (v/v) CF_3COOH solution in CH_2Cl_2 (400 μL). The reaction mixture was allowed to reach 0 $^\circ\text{C}$ and was stirred for 1 h at that temperature. The solvents were evaporated under reduced pressure, and the crude product was purified by preparative thin-layer chromatography (silica gel, 6% MeOH in CH_2Cl_2) to afford pure dihydroxy lactone 3 (31 mg, 92%): $R_f = 0.38$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -80.2$ (c 1.7, CHCl_3); IR (thin film) ν_{max} 3470, 2929, 1733, 1686, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 6.83 (s, 1 H, $\text{SCH}=\text{C}$), 6.56 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.48 (dd, $J = 7.0, 3.0$ Hz, 1 H, $\text{O}=\text{COCH}$), 5.43–5.41 (m, 2 H, $\text{CH}=\text{CH}$), 4.21 (d, $J = 11.5$ Hz, 1 H, CHOH), 3.77 (bs, 1 H, CHOH), 3.13 (bs, 1 H, OH), 3.01 (bs, 1 H, OH), 2.95 (m, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.70–2.62 (m, 1 H, CH_2COO), 2.47 (ddd, $J = 14.6, 11.5$ Hz, 1 H, CH_2COO), 2.27 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.18–2.12 (m, 2 H, $\text{CH}=\text{CHCH}_2$), 2.15 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.97–1.83 (m, 2 H, $\text{CH}_2\text{CH}=\text{CH}$), 1.56–1.50 (m, 1 H, $\text{CH}(\text{CH}_3)$), 1.41–1.22 (m, 4 H, 2 \times CH_2), 1.15 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.07 (d, $J = 6.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.07 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.06 (s, 3 H, $\text{C}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, C_6D_6) δ 220.2, 170.6, 165.4, 153.8, 139.2, 134.1, 126.1, 120.4, 116.9, 79.2, 74.9, 73.2, 54.2, 42.5, 40.3, 39.5, 32.9, 32.6, 28.6, 28.4, 23.3, 19.3, 19.1, 16.4, 16.3, 14.4; FAB HRMS (NBA/CsI) m/e 610.1580, $\text{M} + \text{Cs}^+$ calcd for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$ 610.1603.

Dihydroxy Lactone 43. Lactone 42 (38.0 mg, 0.054 mmol) was treated with CF_3COOH in exactly the same way as described above for 3, yielding dihydroxy lactone 43 (24.5 mg, 95%): $R_f = 0.30$ (silica gel, 6% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -93.1$ (c 0.1, CHCl_3); IR (thin film) ν_{max} 3450, 2929, 1735, 1685, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.96 (s, 1 H, $\text{SCH}=\text{C}$), 6.51 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.60–5.50 (m, 2 H, $\text{CH}=\text{CH}$), 5.40–5.32 (m, 1 H, $\text{O}=\text{COCH}$), 4.25 (d, $J = 9.5$ Hz, 1 H, CHOH), 3.55 (d, $J = 9.6$ Hz, 1 H, CHOH), 3.39 (bs, 1 H, OH), 3.31 (dq, $J = 6.9, 6.7$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.99 (bs, 1 H, OH), 2.71 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.69–2.61 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 2.59 (d, $J = 16.3$ Hz, 1 H, CH_2COO), 2.45–2.35 (m, 2 H, CH_2COO , $\text{CH}=\text{CHCH}_2$), 2.20–2.10 (m, 1 H, $\text{CH}_2\text{CH}=\text{CH}$), 2.08 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.98–1.90 (m, 1 H, $\text{CH}_2\text{CH}=\text{CH}$), 1.59–1.50 (m, 1 H, $\text{CH}(\text{CH}_3)$), 1.49–1.30 (m, 4 H, 2 \times CH_2), 1.17 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.11 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.03 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.01 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 222.2, 171.1, 165.2, 153.5, 139.5, 133.2, 125.1, 120.0, 116.7, 78.4, 74.1, 72.9, 52.5, 40.7, 39.5, 37.9, 34.5, 32.7, 31.3, 27.6, 24.7, 22.2, 18.9, 17.5, 15.5, 15.3; FAB HRMS (NBA) m/e 478.2610, $\text{M} + \text{H}^+$ calcd for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$ 478.2627.

Epothilone A (1). Epoxidation of Lactone 3 with Methyl-(trifluoromethyl)dioxirane. To a solution of 3 (10 mg, 21.0 μmol) in MeCN (200 μL) was added 4×10^{-4} M aqueous solution of disodium ethylenediaminetetraacetate (Na_2EDTA , 120 μL), and the reaction mixture was cooled to 0 $^\circ\text{C}$. 1,1,1-Trifluoroacetone (200 μL) was added followed by a mixture of Oxone (61 mg, 0.10 mmol, 5.0 equiv) and NaHCO_3 (14.0 mg, 0.17 mmol, 8.0 equiv) with stirring until completion of the reaction was revealed by TLC. The reaction mixture was treated with excess Me_2S (100 μL) and water (500 μL) and was then extracted with EtOAc (4 \times 2 mL). The combined organic phase was dried (MgSO_4), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave a mixture of epothilones A (1) and its α -epoxide epimer (8.6 mg, 78% total yield). A second preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) furnished pure epothilone A (1) (6.4 mg, 65%) as a white solid. For a more extensive study of the epoxidation of 3 and isolation of a number of epothilone A analogues, see ref 29. 1: $R_f = 0.23$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -45.0$ (c 0.02, MeOH); IR (thin film) ν_{max} 3476, 2974, 1738, 1692 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) δ 6.71 (s, 1 H, $\text{CH}=\text{CCH}_3$), 6.45 (s, 1 H, $\text{SCH}=\text{C}$), 5.45 (dd, $J = 8.2, 2.3$ Hz, 1 H, $\text{O}=\text{COCH}$), 4.15 (dd, $J = 10.8, 2.9$ Hz, 1 H, CHOH), 3.81–3.78 (m, 1 H, CHOH), 3.65 (bs, 1 H, OH), 3.03 (dq, $J = 6.9, 6.5$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.77 (ddd, $J = 7.9, 4.0, 4.0$ Hz, 1 H, CH_2CHO), 2.62–2.58 (m, 1 H, CH_2CHO), 2.40 (dd, $J = 14.4, 10.8$ Hz, 1 H, CH_2COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.19 (dd, $J = 14.4, 2.9$ Hz, 1 H, CH_2COO), 2.05 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.86 (ddd, $J = 15.2, 2.5, 2.5$ Hz, 1 H, CH_2CHO), 1.81–1.74

(m, 1 H, CH_2CHO), 1.68 (ddd, $J = 15.2, 7.6, 7.6$ Hz, 1 H, CH_2CHO), 1.53–1.49 (m, 1 H, CH_2CHO), 1.40–1.15 (m, 5 H, $\text{CH}(\text{CH}_3)_2$, 2 \times CH_2), 1.06 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$), 1.03 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 0.97 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 0.95 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, C_6D_6) δ 219.0, 170.2, 164.7, 153.0, 137.5, 119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8, 39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6, 18.7, 17.4, 15.7, 14.6; HRMS (FAB), calcd for $\text{C}_{26}\text{H}_{39}\text{CsNO}_6\text{S}$ ($\text{M} + \text{Cs}^+$) 626.1552, found 626.1531.

6S,7R-Epothilones 44 and 45. Epoxidation of Lactone 43. To a solution of lactone 43 (9.0 mg, 18.8 μmol) in MeCN (0.5 mL) were added disodium ethylenediaminetetraacetate (Na_2EDTA , 4×10^{-4} M aqueous solution, 200 μL) and 1,1,1-trifluoroacetone (200 μL) at 0 $^\circ\text{C}$. The resulting solution was stirred at 0 $^\circ\text{C}$, while a mixture of solid Oxone (58 mg, 94.0 mmol, 5.0 equiv) and NaHCO_3 (14.0 mg, 0.17 mmol, 8.8 equiv) was added portionwise until completion of the reaction was established by TLC. The reaction mixture was treated with excess Me_2S (100 μL) and water (500 μL) and was extracted with EtOAc (4 \times 2 mL). The combined organic phase was dried (MgSO_4), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave a mixture of epothilones 44 and 45 (8.1 mg, 87% total yield, ca. 2:1 ratio by ^1H NMR). The major diastereoisomer (44, stereochemistry unassigned) was isolated by preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) (5.4 mg, 58%) and exhibited the following properties: $R_f = 0.23$ (silica gel, 6% MeOH in CH_2Cl_2); $[\alpha]_D^{20} -20.0$ (c 0.2, CHCl_3); IR (thin film) ν_{max} 3448, 2919, 1725, 1684, 1455, 1378, 1284, 1149, 1061, 1020, 973, 750 cm^{-1} ; ^1H NMR (500 MHz, CHCl_3) δ 6.99 (s, 1 H, $\text{SCH}=\text{C}$), 6.68 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.64–5.61 (m, 1 H, $\text{O}=\text{COCH}$), 4.43 (d, $J = 2.1$ Hz, 1 H, OH), 4.29 (ddd, $J = 7.6, 2.5, 2.5$ Hz, 1 H, CHOH), 3.82 (d, $J = 8.2$ Hz, 1 H, CHOH), 3.35 (bs, 1 H, OH), 3.22 (q, $J = 7.0$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 3.14 (ddd, $J = 10.3, 4.1, 3.2$ Hz, 1 H, CH_2CHO), 2.90 (ddd, $J = 10.3, 4.3, 2.3$ Hz, 1 H, CH_2CHO), 2.71 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.54 (dd, $J = 13.7, 7.6$ Hz, 1 H, CH_2COO), 2.51 (dd, $J = 13.7, 2.5$ Hz, 1 H, CH_2COO), 2.21–2.19 (m, 1 H, CH_2CHO), 2.18 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)_2$), 1.94 (ddd, $J = 15.3, 10.3, 3.7$ Hz, 1 H, CH_2CHO), 1.77–1.69 (m, 2 H, CH_2CHO), 1.60–1.00 (m, 5 H, $\text{CH}(\text{CH}_3)_2$, 2 \times CH_2), 1.15 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 1.14 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$), 1.06 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 1.02 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CHCl_3) δ 221.8, 172.1, 165.1, 152.6, 134.7, 119.8, 116.8, 76.0, 74.4, 72.8, 56.4, 53.8, 53.0, 40.2, 39.1, 34.1, 32.7, 29.4, 27.8, 22.7, 20.9, 19.0, 16.1, 15.9, 15.0, 11.8; FAB HRMS (NBA) m/e 494.2587, $\text{M} + \text{H}^+$ calcd for $\text{C}_{26}\text{H}_{39}\text{NO}_6\text{S}$ 494.2576.

Olefinic Compound 48. Phosphonium salt 12 (9.0 g, 12.93 mmol, 1.5 equiv) was dissolved in THF (90 mL), and the solution was cooled to 0 $^\circ\text{C}$. Sodium bis(trimethylsilyl)amide (NaHMDS , 1.0 M solution in THF, 12.84 mL, 12.84 mmol, 1.48 equiv) was slowly added, and the resulting mixture was stirred at 0 $^\circ\text{C}$ for 15 min. The reaction mixture was then cooled to -20 $^\circ\text{C}$ before ketone 11 (2.23 g, 8.62 mmol, 1.0 equiv) in THF (10 mL) was added, and the reaction mixture was stirred at the same temperature for 12 h. Saturated aqueous NH_4Cl solution (50 mL) was added, and the mixture was extracted with ether (200 mL). The organic phase was washed with brine (2 \times 100 mL), dried (MgSO_4), and concentrated to afford, after flash column chromatography (silica gel, 2% ether in hexanes), olefins 48 (3.8 g, 73%, $Z:E$ ca. 1:1 by ^1H NMR).

Hydroxy Olefins 49. Desilylation of Silyl Ether 48. Silyl ether 48 (3.80 g, 6.88 mmol) was dissolved in $\text{CH}_2\text{Cl}_2:\text{MeOH}$ (1:1, 70 mL), and the solution was cooled to 0 $^\circ\text{C}$ prior to addition of CSA (1.68 g, 7.23 mmol, 1.05 equiv) during a 5 min period. The resulting mixture was stirred for 30 min at 0 $^\circ\text{C}$ and then for 1 h at 25 $^\circ\text{C}$. Et_3N (1.57 mL, 7.23 mmol, 1.05 equiv) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished pure hydroxy compound 49 (2.9 g, 97%).

Aldehyde 8'. Oxidation of Alcohol 49. Alcohol 49 (mixtures of Z and E geometrical isomers, 4.60 g, 10.64 mmol) was dissolved in CH_2Cl_2 (105 mL, 0.1 M). DMSO (35 mL), Et_3N (7.4 mL, 53.20 mmol, 5.0 equiv), and $\text{SO}_3\cdot\text{pyr}$ (3.4 g, 21.28 mmol, 2.0 equiv) were added at 25 $^\circ\text{C}$, and the resulting mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (50 mL) and ether (300 mL) were added, and the organic phase was separated and washed with brine (2 \times 30 mL), dried (MgSO_4), and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) furnished aldehyde

Tris(silyl ethers) 52' and 53'. Aldol Reaction of Keto Acid 9 with Aldehyde 8'. A solution of keto acid 9 (773 mg, 2.56 mmol, 1.2 equiv) in THF (7.0 mL) was reacted with aldehyde 8' (930 mg, mixture of $Z:E$ olefins, ca. 1:1, 2.13 mmol, 1.0 equiv) according to the same procedure as described above for the condensation of 9 and 7, to afford, after similar processing, pure carboxylic acids 52' (564 mg, mixture of Z and E isomers, ca. 1:1, 31% from 8') and 53' (545 mg, mixture of Z and E isomers, ca. 1:1, 30% from 8') as colorless oils and recovered keto acid 9 (125 mg).

Hydroxy Acid 6'. Selective Desilylation of 52'. Carboxylic acid 52' (300 mg, mixture of Z and E isomers, ca. 1:1, 0.35 mmol) was converted to hydroxy acid 6' (194 mg, mixture of Z and E isomers, ca. 1:1, 75%) according to the same procedure described above for hydroxy acid 5.

Lactones 54 and 55. Macrolactonization of Hydroxy Acid 6'. A solution of hydroxy acid 6' (140 mg, mixture of Z and E isomers, ca. 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 $^\circ\text{C}$ with Et_3N (58 μL , 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 μL , 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 $^\circ\text{C}$ for 1 h and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 $^\circ\text{C}$ and stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration followed by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure lactones 54 (50 mg, 37%) and 55 (54 mg, 40%) as colorless oils. 54: $R_f = 0.40$ (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]_D^{20} -11.8$ (c 0.8, CHCl_3); IR (thin film) ν_{max} 2931, 2848, 1737, 1690, 1461, 1378, 1249, 1184, 1158, 1097, 1020, 984, 835, 775 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.95 (s, 1 H, $\text{SCH}=\text{C}$), 6.56 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.16 (dd, $J = 8.4, 7.5$ Hz, 1 H, $\text{CH}_2\text{C}=\text{CHCH}_2$), 4.96 (d, $J = 10.1$ Hz, 1 H, CH_2COOCH), 4.02 (d, $J = 9.9$ Hz, 1 H, CHOSi), 3.88 (d, $J = 8.9$ Hz, 1 H, CHOSi), 3.02 (dq, $J = 6.9, 6.7$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.79 (d, $J = 15.6$ Hz, 1 H, CH_2COOCH), 2.70 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.70–2.65 (m, 2 H), 2.48–2.40 (m, 1 H), 2.10 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)_2$), 2.10–2.04 (m, 2 H), 1.75–1.69 (m, 2 H), 1.67 (s, 3 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.66–1.45 (m, 3 H), 1.18 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 1.13 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 1.09 (d, $J = 6.8$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$), 0.97 (d, $J = 6.8$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$), 0.94 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.84 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.10 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.07 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), -0.12 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 215.1, 171.2, 164.6, 152.5, 140.6, 138.8, 119.3, 119.1, 115.9, 79.9, 76.3, 53.4, 39.1, 32.4, 31.9, 31.4, 29.7, 27.4, 26.4, 26.1, 26.0, 24.5, 24.3, 23.1, 19.2, 18.7, 18.6, 17.8, 15.3, -3.3 , -3.7 , -5.7 ; FAB HRMS (NBA) m/e 720.4534, $\text{M} + \text{H}^+$ calcd for $\text{C}_{30}\text{H}_{49}\text{NO}_6\text{Si}_2$ 720.4513. 55: $R_f = 0.50$ (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]_D^{20} -22.7$ (c 0.6, CHCl_3); IR (thin film) ν_{max} 2931, 2860, 1731, 1696, 1461, 1378, 1249, 1179, 1079, 985, 832, 773 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.92 (s, 1 H, $\text{SCH}=\text{C}$), 6.53 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.27 (dd, $J = 8.0, 2.7$ Hz, 1 H, CH_2COOCH), 5.16 (dd, $J = 6.9, 6.6$ Hz, 1 H, $\text{CH}_2\text{C}=\text{CHCH}_2$), 4.47 (t, $J = 5.1$ Hz, 1 H, CHOSi), 3.89 (dd, $J = 4.5, 1.0$ Hz, 1 H, CHOSi), 3.05 (dq, $J = 6.7, 6.2$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.70 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.60 (dd, $J = 15.8, 5.8$ Hz, 1 H, CH_2COOCH), 2.55 (m, 1 H, $\text{CH}_2\text{C}=\text{CHCH}_2$), 2.51–2.47 (m, 2 H, CH_2COOCH , $\text{CH}_2\text{C}=\text{CHCH}_2$), 2.13 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)_2$), 2.10–2.05 (m, 1 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.91 (m, 1 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.68–1.45 (m, 4 H), 1.57 (s, 3 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.27–1.23 (m, 1 H), 1.17 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 1.04 (d, $J = 6.8$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$), 1.07 (s, 3 H, $\text{C}(\text{CH}_3)_3$), 0.93 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)_2$), 0.88 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.86 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.07 (s, 6 H, $\text{Si}(\text{CH}_3)_2$), 0.06 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 217.2, 171.3, 165.5, 153.6, 139.0, 138.3, 120.9, 120.2, 117.0, 80.1, 77.2, 73.9, 54.8, 44.9, 42.7, 41.1, 40.2, 32.8, 26.9, 26.8, 25.6, 23.5, 21.1, 20.1, 19.2, 19.1, 17.7, 16.8, 16.6, 16.3, -2.7 , -3.1 , -3.4 , -3.6 ; FAB HRMS (NBA) m/e 720.4533, $\text{M} + \text{H}^+$ calcd for $\text{C}_{30}\text{H}_{49}\text{NO}_6\text{Si}_2$ 720.4513.

Dihydroxy Lactone 4. Dihydroxy lactone 4 was prepared from bis(silyl ether) lactone 54 (13.3 mg, 0.018 mmol) by treatment with CF_3COOH according to the same procedure described above for the preparation of 3, to obtain pure lactone 4 (8.4 mg, 91%) as a colorless oil. 4: $R_f = 0.21$ (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]_D^{20} -91.5$ (c 0.3, CHCl_3); IR (thin film) ν_{max} 3460, 2954, 2919, 1725, 1684, 1455, 1379, 1290, 1249, 1184, 1143, 1043, 1008, 973, 750 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.94 (s, 1 H, $\text{SCH}=\text{C}$), 6.57 (s, 1 H, $\text{CH}=\text{CCH}_3$),

5.20 (d, $J = 9.7$ Hz, 1 H, CH_2COOCH), 5.13 (dd, $J = 9.6, 4.6$ Hz, 1 H, $\text{CH}_3\text{C}=\text{CHCH}_2$), 4.28 (d, $J = 9.7$ Hz, 1 H, $(\text{CH}_3)_2\text{CCHOH}$), 3.71 (s, 1 H, CHOH), 3.47 (bs, 1 H, OH), 3.15 (q, $J = 6.8$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 3.04 (bs, 1 H, OH), 2.68 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.62 (ddd, $J = 15.0, 10.2, 10.1$ Hz, 1 H, $\text{CH}_2\text{CH}=\text{CCH}_3$), 2.45 (dd, $J = 14.7, 11.1$ Hz, 1 H, CH_2COOCH), 2.38–2.24 (m, 1 H), 2.28 (dd, $J = 14.8, 2.2$ Hz, CH_2COOCH), 2.22 (d, $J = 14.9$ Hz, 1 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CHCH}_2$), 2.06 (s, 3 H, $\text{CH}=\text{CCH}_3$), 1.90–1.84 (m, 1 H), 1.76–1.69 (m, 1 H), 1.65 (s, 3 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.33 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.32–1.22 (m, 4 H), 1.19 (d, $J = 6.8$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.06 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.00 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 220.4, 170.2, 164.9, 151.8, 139.1, 138.3, 120.8, 119.1, 115.5, 78.9, 74.1, 72.3, 53.6, 41.7, 39.7, 32.6, 31.8, 31.7, 25.4, 23.0, 19.1, 18.1, 16.0, 15.8, 13.5; FAB HRMS (NBA) m/e 492.2795, $M + H^+$ calcd for $\text{C}_{27}\text{H}_{41}\text{NO}_6$ 492.2784.

Dihydroxy Lactone 56. Dihydroxy lactone 56 was prepared from bis(silyl ether) lactone 55 (40.0 mg, 0.055 mmol) by treatment with CF_3COOH according to the same procedure described above for the preparation of 3. Obtained pure 56 (24.3 mg, 89%); $R_f = 0.19$ (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -61.0$ (c 0.2, CHCl_3); IR (thin film) ν_{max} 3418, 2932, 1731, 1691, 1466, 1381, 1252, 1159, 1067, 1044, 1012, 978, 755 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.99 (s, 1 H, $\text{SCH}=\text{C}$), 6.54 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.38 (dd, $J = 6.7, 3.8$ Hz, 1 H, CH_2COOCH), 5.08 (t, $J = 6.9$ Hz, 1 H, $\text{CH}_3\text{C}=\text{CHCH}_2$), 4.32 (dd, $J = 10.0, 2.4$ Hz, 1 H, $(\text{CH}_3)_2\text{CCHOH}$), 3.65 (t, $J = 3.4$ Hz, 1 H, CHOH), 3.25 (dq, $J = 6.7, 3.9$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.68 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.55–2.43 (m, 3 H, CH_2COOCH , $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 2.40 (dd, $J = 15.3, 2.5$ Hz, 1 H, CH_2COOCH), 2.17–2.10 (m, 1 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 2.05 (s, 3 H, $\text{CH}=\text{CCH}_3$), 1.95 (ddd, $J = 13.4, 10.0, 3.3$ Hz, 1 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.70–1.57 (m, 3 H), 1.57 (s, 3 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.50–1.35 (m, 2 H), 1.33 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.15 (d, $J = 6.8$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.03 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 0.97 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 220.7, 170.7, 165.3, 152.3, 138.5, 137.4, 119.6, 119.4, 115.7, 77.7, 76.2, 71.6, 52.7, 42.7, 39.4, 39.0, 37.3, 30.7, 24.5, 19.5, 19.7, 18.7, 15.9, 15.8, 15.5, 14.3; FAB HRMS (NBA) m/e 492.2772, $M + H^+$ calcd for $\text{C}_{27}\text{H}_{41}\text{NO}_6$ 492.2784.

Epothilone B (2) and Its α -Epoxide Epimer 57. Epoxidation of Lactone 4. **Procedure A:** To a solution of lactone 4 (3.0 mg, 6.1 μmol) in benzene (0.2 mL) at -10°C was added *m*-chloroperbenzoic acid (2.9 mg, 50–60% purity, 8.4–10.1 μmol , 1.4–1.6 equiv), and the reaction mixture was stirred at that temperature for 2 h, at which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous NaHCO_3 solution (2 mL), and the aqueous phase was extracted with EtOAc (3 \times 2 mL). The combined organic layer was dried (MgSO_4), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) provided a mixture of epothilone B (2) and its α -epoxy diastereoisomer 57 (2.0 mg, 66%, ca. 5:1 ratio by ^1H NMR), which was separated to its components by a second preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) furnishing pure epothilone B (2) (1.6 mg, 52%) as a white solid. **Procedure B:** To a solution of lactone 4 (5.0 mg, 10.2 μmol) in CH_2Cl_2 (0.5 mL) at -50°C was added dropwise a solution of dimethyldioxirane in acetone until the starting material disappeared (TLC). The resulting solution was concentrated, and the crude product was subjected to preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give epothilone B (2) and its α -epoxy diastereoisomer 57 in ca. 5:1 ratio (3.9 mg, 75%). Pure epothilone B (2) was obtained (3.1 mg, 60%) by preparative thin-layer chromatography as described above. **Procedure C:** Lactone 4 (3.0 mg, 6.1 μmol) was epoxidized with methyl(trifluoromethyl)dioxirane according to the procedure described above for the epoxidation of 3, to yield a mixture of 2 and its α -epoxy diastereoisomer 57 in ca. 5:1 ratio by ^1H NMR (2.6 mg, 85% yield). The major diastereoisomer, epothilone B (2), was isolated as described above (2.1 mg, 69%). 2: colorless crystals; mp 93°C (crystallized in CH_2Cl_2 /petroleum ether); $R_f = 0.24$ (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -34.3$ (c 0.2, MeOH); IR (thin film) ν_{max} 3436, 2954, 2931, 1731, 1684, 1455, 1373, 1290, 1249, 1184, 1143, 1043, 1049, 973, 750 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.97 (s, 1 H, $\text{SCH}=\text{C}$), 6.59 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.41 (dd, $J = 7.8, 2.8$ Hz, 1 H, CH_2COOCH), 4.22 (bs, 2 H, $(\text{CH}_3)_2\text{CCHOH}$, OH), 3.77 (dd, $J = 4.3, 4.2$ Hz, 1 H, CHOH), 3.30 (dq, $J = 6.8, 4.1$ Hz, 1 H, $\text{C}(\text{O})$

CHCH_3), 2.80 (dd, $J = 7.6, 4.7$ Hz, 1 H, CHOCCH_3), 2.70 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.64 (bs, 1 H, OH), 2.54 (dd, $J = 14.0, 10.2$ Hz, 1 H, CH_2COOCH), 2.36 (d, $J = 14.0, 2.9$ Hz, 1 H, CH_2COOCH), 2.12 (dd, $J = 4.7, 2.8$ Hz, 1 H, $(\text{CH}_3)\text{COCHCH}_2\text{CHO}$), 2.08 (s, 3 H, $\text{CH}=\text{CCH}_3$), 1.91 (ddd, $J = 15.4, 7.8, 7.6$ Hz, 1 H, $(\text{CH}_3)\text{COCHCH}_2\text{CHO}$), 1.77–1.68 (m, 3 H), 1.53–1.46 (m, 2 H), 1.43–1.37 (m, 2 H), 1.36 (s, 3 H, $\text{C}(\text{CH}_3)\text{OCHCH}_2$), 1.27 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.16 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.08 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.00 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$); ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 7.34 (s, 1 H, $\text{SCH}=\text{C}$), 6.49 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.27 (dd, $J = 9.0, 2.0$ Hz, 1 H, CH_2COOCH), 5.07 (d, $J = 6.9$ Hz, 1 H, OH), 4.45 (bs, 1 H, OH), 4.08 (m, 1 H, $(\text{CH}_3)_2\text{CCHOH}$), 3.47 (d, $J = 7.4$ Hz, 1 H, CHOH), 3.10 (dq, $J = 6.8, 6.5$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.81 (dd, $J = 9.5, 3.3$ Hz, 1 H, CHOCCH_3), 2.64 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.40–2.30 (m, 2 H, CH_2COOCH), 2.08 (s, 3 H, $\text{CH}=\text{CCH}_3$), 2.05 (ddd, $J = 15.0, 2.6, 1.0$ Hz, 1 H, $(\text{CH}_3)\text{COCHCH}_2\text{CHO}$), 1.83 (ddd, $J = 15.0, 9.3, 9.1$ Hz, 1 H, $(\text{CH}_3)\text{COCHCH}_2\text{CHO}$), 1.61 (m, 1 H), 1.45–1.35 (m, 3 H), 1.35–1.25 (m, 3 H), 1.17 (s, 6 H, $\text{C}(\text{CH}_3)\text{OCHCH}_2$, $\text{C}(\text{CH}_3)_2$), 1.05 (d, $J = 6.6$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.87 (d, $J = 7.0$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.86 (s, 3 H, $\text{C}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, $\text{DMSO}-d_6$) δ 218.1, 170.7, 164.8, 152.5, 137.6, 119.5, 118.0, 76.7, 75.7, 70.7, 61.6, 61.1, 53.3, 44.9, 35.6, 33.0, 32.1, 29.6, 23.0, 22.4, 22.0, 19.7, 18.8, 18.4, 16.4, 14.1; FAB HRMS (NBA/CsI) m/e 640.1725, $M + \text{Cs}^+$ calcd for $\text{C}_{27}\text{H}_{41}\text{NO}_6\text{S}$ 640.1709. A natural sample³⁰ of epothilone B (2) exhibited properties identical to those reported above.

Epothilone 58 and 59. Epoxidation of Lactone 56. **Procedure A:** Compound 56 (5.0 mg, 10.2 μmol) was epoxidized with *m*CPBA according to procedure A described above for 2 to yield a mixture of 12*S*-epi-epothilone B (58) and its α -epoxy diastereoisomer 59 (3.7 mg, 73% total yield, ca. 1:4 by ^1H NMR). Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure 12*R*-epothilone 59 (2.5 mg, 49%) as a white solid. **Procedure B:** The epoxidation of 56 (3.0 mg, 6.1 μmol) according to the procedure described above for 1 led to epothilones 58 and its α -epoxy diastereoisomer 59 (2.6 mg, 86% total yield, ca. 1:1 ratio by ^1H NMR). Preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) furnished pure epothilone 58 (1.3 mg, 43%) and its α -epoxy diastereoisomer 59 (1.3 mg, 43%). 58: $R_f = 0.52$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -33.1$ (c 0.1, CHCl_3); ^1H NMR (600 MHz, C_6D_6) δ 6.62 (s, 1 H, $\text{CH}=\text{CCH}_3$), 6.44 (s, 1 H, $\text{SCH}=\text{C}$), 5.46 (dd, $J = 7.2, 5.1$ Hz, 1 H, CH_2COOCH), 4.22 (dd, $J = 8.3, 3.0$ Hz, 1 H, $(\text{CH}_3)_2\text{CCHOH}$), 3.71 (dd, $J = 4.2, 3.6$ Hz, 1 H, CHOH), 3.10 (dq, $J = 8.6, 3.7$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.95 (bs, 1 H, OH), 2.86 (dd, $J = 5.8, 5.7$ Hz, 1 H, CHOCCH_3), 2.82 (bs, 1 H, OH), 2.30 (dd, $J = 14.8, 10.1$ Hz, 1 H, CH_2COOCH), 2.24 (dd, $J = 14.8, 3.5$ Hz, 1 H, CH_2COOCH), 2.19 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 1.99 (s, 3 H, $\text{CH}=\text{CCH}_3$), 1.79–1.75 (m, 2 H), 1.74–1.70 (m, 1 H, $(\text{CH}_3)\text{COCHCH}_2\text{CHO}$), 1.60–1.55 (m, 1 H), 1.37–1.20 (m, 3 H), 1.18–1.11 (m, 1 H), 1.05 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.04 (s, 6 H, $\text{C}(\text{CH}_3)\text{OCHCH}_2$, $\text{C}(\text{CH}_3)_2$), 0.92 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 0.85 (d, $J = 7.1$ Hz, 3 H, $\text{CH}(\text{CH}_3)$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 220.3, 170.8, 134.0, 133.8, 132.3, 128.7, 116.3, 73.7, 72.2, 61.5, 59.7, 53.0, 42.5, 38.7, 38.4, 36.7, 32.4, 32.1, 22.5, 21.4, 19.5, 17.8, 15.7, 15.4, 13.9, 12.5. 59: $R_f = 0.55$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} -34.5$ (c 0.1, CHCl_3); IR (thin film) ν_{max} 3440, 2929, 1731, 1693, 1467, 1384, 1294, 1257, 1151, 1050, 977, 755 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.97 (s, 1 H, $\text{SCH}=\text{C}$), 6.60 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.50 (dd, $J = 8.0, 4.0$ Hz, 1 H, CH_2COOCH), 4.25 (dd, $J = 10.1, 3.2$ Hz, 1 H, $(\text{CH}_3)_2\text{CCHOH}$), 3.80 (bs, 1 H, OH), 3.75 (dd, $J = 5.5, 3.6$ Hz, 1 H, CHOH), 3.31 (dq, $J = 6.7, 6.3$ Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.88 (dd, $J = 6.3, 4.5$ Hz, 1 H, CHOCCH_3), 2.69 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.59 (bs, 1 H, OH), 2.55 (dd, $J = 13.5, 10.4$ Hz, 1 H, CH_2COOCH), 2.45 (dd, $J = 13.5, 3.7$ Hz, 1 H, CH_2COOCH), 2.08 (s, 3 H, $\text{CH}=\text{CCH}_3$), 2.05–1.97 (m, 3 H), 1.95–1.90 (m, 1 H, $(\text{CH}_3)\text{COCHCH}_2\text{CHO}$), 1.75–1.70 (m, 2 H), 1.51–1.45 (m, 3 H), 1.37 (s, 3 H, $\text{C}(\text{CH}_3)\text{OCHCH}_2$), 1.27 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.14 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.04 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 0.95 (d, $J = 6.9$ Hz, 3 H, $\text{CH}(\text{CH}_3)$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 219.6, 170.7, 164.9, 152.1, 136.6, 119.8, 116.4, 77.6, 75.9, 73.3, 61.3, 59.9, 52.9, 44.2, 38.8, 37.2, 36.4, 32.9, 31.3, 21.9, 21.3, 19.8, 19.4, 17.9, 17.4, 14.8; FAB HRMS (NBA/CsI) m/e 640.1686, $M + \text{Cs}^+$ calcd for $\text{C}_{27}\text{H}_{41}\text{NO}_6\text{S}$ 640.1709.

α,β -Unsaturated Ester 60. A mixture of aldehyde 15 (5.17 g, 15.9 mmol) and stabilized ylide 16 (8.92 g, 24.0 mmol, 1.5 equiv, prepared from 4-bromo-1-butene by (i) phosphonium salt formation, (ii) anion

formation with NaHMDS, and (iii) quenching with MeOC(O)Cl³²) in benzene (300 mL, 0.05 M) was heated at reflux for 3 h. After being cooled to 25 °C, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 30% ether in hexanes) to afford α,β -unsaturated ester **60** (7.15 g, 95%); R_f = 0.65 (silica gel, 40% ether in hexanes); $[\alpha]_D^{25}$ +10.4 (c 1.4, CHCl₃); IR (thin film) ν_{\max} 2939, 2856, 1715, 1644, 1504, 1464, 1437, 1365, 1284, 1252, 1209, 1076, 955, 836, 776 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.87 (d, J = 7.4 Hz, 1 H, CH=CCH₃), 6.47 (s, 1 H, CH=CCH₃), 5.83–5.71 (m, 1 H, CH=CH₂), 5.01–4.92 (m, 2 H, CH=CH₂), 4.19 (dd, J = 7.7, 4.9 Hz, 1 H, CHOSi), 3.69 (s, 3 H, COOCH₃), 3.05 (d, J = 6.0 Hz, 2 H, CH₂CH=CH₂), 2.67 (s, 3 H, N=C(S)CH₃), 2.46 (ddd, J = 15.1, 7.7, 7.4 Hz, 1 H, CH₂CHOSi), 2.39 (ddd, J = 15.0, 7.5, 5.0 Hz, 1 H, CH₂CHOSi), 1.99 (s, 3 H, CH=CCH₃), 0.86 (s, 9 H, Si(CH₃)₃), 0.03 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 167.8, 164.4, 152.8, 141.5, 140.6, 135.3, 130.7, 119.1, 115.5, 115.1, 77.6, 51.7, 36.1, 30.9, 25.7, 19.2, 18.1, 13.9, -4.7, -5.1; FAB HRMS (NBA) m/e 554.1168, $M + H^+$ calcd for C₂₂H₃₅NO₃Si 554.1161.

Allylic Alcohol 61. Methyl ester **60** (6.1 g, 14.4 mmol) was dissolved in THF (80 mL) and cooled to -78 °C. DIBAL (44.0 mL, 1 M solution in CH₂Cl₂, 44.0 mmol, 3.0 equiv) was added dropwise at -78 °C, and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with MeOH (1.0 mL) at -78 °C, and then ether (100 mL) was added, followed by saturated aqueous sodium-potassium tartrate solution (10 mL). The resulting mixture was allowed to warm to room temperature, where it was stirred for 3 h. The organic layer was separated, and the aqueous phase was extracted with ether (2 \times 50 mL). The combined organic phase was dried (MgSO₄), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 40–80% ether in hexanes) furnished alcohol **61** (5.58 g, 98%); R_f = 0.18 (silica gel, 40% ether in hexanes); $[\alpha]_D^{25}$ +6.6 (c 1.1, CHCl₃); IR (thin film) ν_{\max} 3380, 2928, 2855, 1637, 1505, 1464, 1386, 1253, 1185, 1074, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.88 (s, 1 H, SCH=C), 6.41 (s, 1 H, CH=CCH₃), 5.77–5.69 (m, 1 H, CH=CH₂), 5.48 (dd, J = 7.3, 7.2 Hz, 1 H, CH=CCH₂OH), 5.00 (dd, J = 15.5, 3.3 Hz, 1 H, CH=CH₂), 4.93 (dd, J = 10.0, 3.3 Hz, 1 H, CH=CH₂), 4.12 (dd, J = 6.5, 6.4 Hz, 1 H, CHOSi), 3.97 (s, 2 H, CH₂OH), 2.86–2.76 (m, 2 H, CH₂CH=CH₂), 2.65 (s, 3 H, N=C(S)CH₃), 2.53 (bs, 1 H, OH), 2.36–2.24 (m, 2 H, CH₂CHOSi), 1.94 (s, 3 H, CH=CCH₃), 0.86 (s, 9 H, Si(CH₃)₃), 0.02 (s, 3 H, Si(CH₃)₂), -0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.5, 152.8, 142.0, 138.1, 123.7, 118.7, 115.2, 114.9, 78.3, 66.6, 34.7, 32.4, 25.7, 19.0, 18.1, 13.7, -4.8, -5.0; FAB HRMS (NBA) m/e 394.2232, $M + H^+$ calcd for C₂₁H₃₃NO₂Si 394.2236.

Compound 62. Chlorination of Alcohol 61. Alcohol **61** (3.00 g, 7.60 mmol) was dissolved in CCl₄ (75 mL, 0.1 M), and Ph₃P (4.00 g, 15.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h and cooled to room temperature, and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10% ether in hexanes) furnished pure **62** (2.6 g, 83%); R_f = 0.50 (silica gel, 15% ether in hexanes); $[\alpha]_D^{25}$ +13.7 (c 1.0, CHCl₃); IR (thin film) ν_{\max} 2953, 2928, 2855, 1637, 1504, 1470, 1439, 1387, 1254, 1182, 1075, 953, 917, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.93 (s, 1 H, SCH=C), 6.47 (s, 1 H, CH=CCH₃), 5.77–5.69 (m, 1 H, CH=CH₂), 5.66 (dd, J = 7.5, 7.2 Hz, 1 H, CH₂CH=CCH₂Cl), 5.07 (dd, J = 17.1, 1.6 Hz, 1 H, CH=CH₂), 5.02 (dd, J = 10.1, 1.4 Hz, 1 H, CH=CH₂), 4.14 (dd, J = 7.2, 5.5 Hz, 1 H, CHOSi), 4.02 (s, 2 H, CH₂Cl), 2.99–2.89 (m, 2 H, CH₂CH=CH₂), 2.71 (s, 3 H, N=C(S)CH₃), 2.52–2.27 (m, 2 H, CH₂CHOSi), 1.99 (s, 3 H, CH=CCH₃), 0.88 (s, 9 H, Si(CH₃)₃), 0.05 (s, 3 H, Si(CH₃)₂), 0.00 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.3, 152.9, 141.8, 134.9, 134.7, 128.9, 119.0, 116.2, 115.2, 78.1, 49.9, 35.3, 32.3, 25.8, 19.2, 18.2, 13.9, -4.7, -5.0; FAB HRMS (NBA) m/e 412.1884, $M + H^+$ calcd for C₂₁H₃₄ClNO₂Si 412.1897.

Compound 63. Reduction of 62. Compound **62** (2.60 g, 6.30 mmol) was dissolved in THF (60 mL, 0.1 M) and cooled to 0 °C. LiEt₃BH (12.6 mL, 1.0 M solution in THF, 12.6 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h. Aqueous NaOH (1.0 mL, 3.0 N) solution was added followed by addition of Et₂O (150 mL). The organic phase was washed with brine (2 \times 20 mL), dried (MgSO₄) and concentrated. Flash column chromatography

(silica gel, 20% ether in hexanes) furnished pure **63** (2.38 g, 99%); R_f = 0.60 (silica gel, 15% ether in hexanes); $[\alpha]_D^{25}$ +17.1 (c 0.7, CHCl₃); IR (thin film) ν_{\max} 2928, 2856, 1637, 1505, 1464, 1253, 1181, 1075, 946, 836, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.77–5.68 (m, 1 H, CH=CH₂), 5.22 (dd, J = 7.3, 7.0 Hz, 1 H, CH₂CH=CCH₃), 5.01 (dd, J = 17.1, 3.2 Hz, 1 H, CH=CH₂), 4.96 (dd, J = 10.1, 3.3 Hz, 1 H, CH=CH₂), 4.09 (dd, J = 7.2, 5.9 Hz, 1 H, CHOSi), 2.80 (dd, J = 14.5, 6.5 Hz, 1 H, CH₂CH=CH₂), 2.73–2.68 (m, 1 H, CH₂CH=CH₂), 2.70 (s, 3 H, N=C(S)CH₃), 2.32–2.19 (m, 2 H, CH₂CHOSi), 1.99 (s, 3 H, CH=CCH₃), 1.66 (s, 3 H, CH₂CH=CCH₃), 0.88 (s, 9 H, Si(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.3, 153.2, 142.5, 136.0, 134.4, 122.5, 118.7, 115.1, 114.9, 78.9, 36.6, 35.3, 25.8, 23.5, 19.2, 18.2, 13.9, -4.8, -5.0; FAB HRMS (NBA) m/e 378.2279, $M + H^+$ calcd for C₂₁H₃₃NO₂Si 378.2287.

Primary Alcohol 64. Selective Hydroboration of Olefinic Compound 63. Compound **63** (1.1 g, 2.91 mmol) was dissolved in THF (3.0 mL, 1.0 M), and the solution was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H₂O₂ (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after which time the reaction mixture was diluted with ether (30 mL). The organic solution was separated, and the aqueous phase was extracted with ether (2 \times 15 mL). The combined organic phase was washed with brine (2 \times 5 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash column chromatography (silica gel, 50–80% ether in hexanes) furnished primary alcohol **64** (1.0 g, 91%); R_f = 0.17 (silica gel, 50% ether in hexanes); $[\alpha]_D^{25}$ +3.6 (c 0.2, CHCl₃); IR (thin film) ν_{\max} 3381, 2953, 2929, 2856, 1723, 1660, 1469, 1444, 1376, 1253, 1185, 1073, 941, 837, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H, CH=CCH₃), 5.17 (dd, J = 7.0, 6.9 Hz, 1 H, CH₂CH=CCH₃), 4.11 (dd, J = 7.1, 5.7 Hz, 1 H, CHOSi), 3.59 (dd, J = 6.5, 6.4 Hz, 2 H, CH₂OH), 2.70 (s, 3 H, N=C(S)CH₃), 2.35–2.28 (m, 1 H, CH₂CHOSi), 2.27–2.20 (m, 1 H, CH₂CHOSi), 2.10 (dd, J = 7.6, 7.5 Hz, 2 H, CH₂CH₂CH₂OH), 1.98 (s, 3 H, CH=CCH₃), 1.67 (s, 3 H, CH₂CH=CCH₃), 1.67–1.58 (m, 2 H, CH₂CH₂OH), 0.88 (s, 9 H, Si(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (150.9 MHz, CDCl₃) δ 164.5, 153.0, 142.7, 136.2, 122.2, 118.5, 115.0, 78.9, 62.4, 35.4, 30.7, 28.0, 25.8, 23.3, 19.2, 18.3, 14.0, -4.7, -5.0; FAB HRMS (NBA) m/e 396.2382, $M + H^+$ calcd for C₂₁H₃₇NO₂Si 396.2393.

Iodide 14. Iodide **14** (1.18 g, 92%) was prepared from alcohol **64** (1.0 g, 2.53 mmol) according to the procedure described above for **27**. **14**: Colorless oil; R_f = 0.65 (silica gel, 20% ether in hexanes); $[\alpha]_D^{25}$ +7.5 (c 0.8, CHCl₃); IR (thin film) ν_{\max} 2955, 2930, 2855, 1504, 1462, 1444, 1376, 1360, 1253, 1183, 1074, 942, 837, 776 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH₃), 5.20 (dd, J = 7.3, 7.1 Hz, 1 H, CH₂CH=CCH₃), 4.09 (dd, J = 7.4, 5.5 Hz, 1 H, CHOSi), 3.14 (dd, J = 7.1, 7.0 Hz, 2 H, CH₂I), 2.69 (s, 3 H, N=C(S)CH₃), 2.34–2.27 (m, 1 H, CH₂CHOSi), 2.26–2.19 (m, 1 H, CH₂CHOSi), 2.17–2.03 (m, 2 H), 2.00 (s, 3 H, CH=CCH₃), 1.93–1.86 (m, 2 H), 1.67 (s, 3 H, CH₂CH=CCH₃), 0.88 (s, 9 H, Si(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), -0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 164.2, 153.1, 142.3, 134.6, 123.1, 118.6, 115.0, 78.8, 35.4, 32.6, 31.9, 25.8, 23.4, 19.2, 18.2, 14.0, 6.5, -4.7, -5.0; FAB HRMS (NBA) m/e 506.1422, $M + H^+$ calcd for C₂₁H₃₆IINO₂Si 506.1410.

Hydrazone 65. Alkylation of SAMP Hydrazone 13 with Iodide 14. SAMP hydrazone **13**¹⁵ (337 mg, 0.2 mmol, 2.0 equiv) in THF (2.5 mL) was added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 μ L, 0.20 mmol, 2.0 equiv) was added to *n*-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol, 2.0 equiv) in 2.5 mL of THF at 0 °C] at 0 °C. After being stirred at that temperature for 8 h, the resulting yellow solution was cooled to -100 °C and a solution of iodide **14** (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to -20 °C over 10 h and then poured into saturated aqueous NH₄Cl solution (5 mL) and extracted with ether (3 \times 25 mL). The combined organic extracts were dried (MgSO₄), filtered, and evaporated. Purification by flash column chromatography on silica gel (20–40% ether in hexanes) provided hydrazone **65** (380 mg, 70%, de > 98% by

¹H NMR) as a yellow oil: $R_f = 0.17$ (silica gel, 20% ether in hexanes); $[\alpha]_D^{20} -27.8$ (c 2.6, CHCl₃); IR (thin film) ν_{\max} 2931, 2861, 1724, 1653, 1599, 1499, 1451, 1374, 1249, 1178, 1077, 940, 834, 774, 727, 673 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.48 (d, $J = 6.6$ Hz, 1 H, CNH), 6.44 (s, 1 H, CH=CCH₃), 5.12 (dd, $J = 7.1, 6.9$ Hz, 1 H, CH₂CH=CCH₃), 4.07 (dd, $J = 6.8, 6.2$ Hz, 1 H, CHOSi), 3.55 (dd, $J = 9.1, 3.7$ Hz, 1 H, CH₂OCH₃), 3.41 (dd, $J = 9.1, 6.9$ Hz, 1 H, CH₂OCH₃), 3.36 (s, 3 H, CH₂OCH₃), 3.35–3.32 (m, 2 H, CH₂N), 2.70 (s, 3 H, N=C(S)CH₃), 2.69–2.62 (m, 1 H), 2.31–2.17 (m, 3 H), 2.04–1.84 (m, 5 H), 1.99 (s, 3 H, CH=CCH₃), 1.79–1.72 (m, 1 H), 1.64 (s, 3 H, CH₂CH=CCH₃), 1.41–1.22 (m, 4 H), 1.01 (d, $J = 6.9$ Hz, CHCH₃), 0.88 (s, 9 H, SiC(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), –0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 164.2, 153.1, 144.3, 142.4, 136.6, 121.5, 118.5, 114.8, 78.9, 74.7, 63.4, 59.1, 50.4, 37.0, 35.3, 35.2, 31.8, 26.4, 25.7, 25.4, 23.3, 22.0, 19.1, 18.9, 18.1, 13.8, –4.8, –5.0; FAB HRMS (NBA) m/e 548.3728, M + H⁺ calcd for C₃₀H₃₃N₃O₂SSi 548.3706.

Nitrile 66. Monoperoxyphthalic acid magnesium salt (MMPP·6H₂O, 233 mg, 0.38 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0 °C. Hydrazone 65 (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca. 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous NaHCO₃ solution (5 mL). The organic layer was separated, and the aqueous phase was extracted with ether (10 mL). The combined organic solution was washed with water (5 mL) and brine (5 mL), dried (MgSO₄), and concentrated. Flash column chromatography (silica gel, 50% ether in hexanes) afforded nitrile 66 (53 mg, 80%) as a colorless oil: $R_f = 0.44$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{20} +10.3$ (c 3.2, CHCl₃); IR (thin film) ν_{\max} 2926, 2855, 1503, 1457, 1381, 1250, 1179, 1072, 935, 833, 773, cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.92 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.18 (dd, $J = 7.0, 6.5$ Hz, 1 H, CH₂CH=CCH₃), 4.08 (dd, $J = 6.5, 6.0$ Hz, 1 H, CHOSi), 2.70 (s, 3 H, N=C(S)CH₃), 2.60–2.53 (m, 1 H), 2.30–2.18 (m, 2 H), 2.11–1.97 (m, 2 H), 1.99 (s, 3 H, CH=CCH₃), 1.67 (s, 3 H, CH₂CH=CCH₃), 1.67–1.45 (m, 4 H), 1.29 (d, $J = 6.9$ Hz, CHCH₃), 0.88 (s, 9 H, SiC(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), –0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 164.3, 153.0, 142.3, 135.5, 122.8, 122.4, 118.6, 114.9, 78.4, 35.3, 33.6, 31.1, 25.7, 25.4, 25.1, 23.2, 19.1, 18.1, 17.9, 13.9, –4.8, –5.1; FAB HRMS (NBA) m/e 433.2720, M + H⁺ calcd for C₂₄H₄₀N₂OSSi 433.2709.

Aldehyde 8. Nitrile 66 (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to –78 °C. DIBAL (245 μ L, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at –78 °C, and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca. 1 h). Methanol (150 μ L) and aqueous HCl (150 μ L, 1 N solution) were sequentially added, and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 \times 5 mL), and the combined organic solution was washed with brine (5 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde 8 (44 mg, 82%): $R_f = 0.48$ (silica gel, 50% ether in hexanes); $[\alpha]_D^{20} +14.7$ (c 1.7, CHCl₃); IR (thin film) ν_{\max} 2915, 2859, 1721, 1500, 1455, 1381, 1251, 1183, 1070, 940, 832, 770 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.60 (d, $J = 1.9$ Hz, 1 H, CHO), 6.92 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.16 (dd, $J = 7.1, 7.0$ Hz, 1 H, CH₂CH=CCH₃), 4.08 (dd, $J = 7.0, 5.5$ Hz, 1 H, CHOSi), 2.70 (s, 3 H, N=C(S)CH₃), 2.36–2.18 (m, 3 H), 2.07–2.01 (m, 2 H), 1.99 (s, 3 H, CH=CCH₃), 1.71–1.64 (m, 1 H), 1.66 (d, $J = 1.0$ Hz, 3 H, CH₂CH=CCH₃), 1.43–1.29 (m, 3 H), 1.08 (d, $J = 7.0$ Hz, 3 H, CH₂CH=CCH₃), 0.88 (s, 9 H, SiC(CH₃)₃), 0.04 (s, 3 H, Si(CH₃)₂), –0.01 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 205.0, 164.4, 153.1, 142.3, 135.9, 122.0, 118.6, 114.9, 78.8, 46.1, 35.3, 31.7, 30.2, 25.7, 25.1, 23.3, 19.1, 18.2, 13.8, 13.2, –4.8, –5.1; FAB HRMS (NBA) m/e 436.2717, M + H⁺ calcd for C₂₄H₄₁NO₂SSi 436.2706.

12Z-Carboxylic Acids 52 and 53. Aldol Reaction of Keto Acid 9 with 12Z-Aldehyde 8. A solution of keto acid 9 (365 mg, 1.21 mmol, 1.6 equiv) in THF (5.0 mL) was reacted with 12Z-aldehyde 8 (330 mg, 0.76 mmol, 1.0 equiv) according to the same procedure as described above for the condensation of 9 and 8 to afford, after similar

processing, geometrically pure 12Z-carboxylic acids 52 (207 mg, 32%) and 53 (181 mg, 28%) and recovered 9. **12Z-Carboxylic acid 52:** $R_f = 0.56$ (silica gel, 5% MeOH in CH₂Cl₂); $[\alpha]_D^{20} -2.9$ (c 0.8, CHCl₃); IR (thin film) ν_{\max} 2933, 2854, 1708, 1464, 1385, 1249, 1187, 1079, 983, 830, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.92 (s, 1 H, SCH=C), 6.58 (s, 1 H, CH=CCH₃), 5.15 (dd, $J = 7.4, 7.1$ Hz, 1 H, (CH₃)₂C=CHCH₂), 4.39 (dd, $J = 6.7, 3.0$ Hz, 1 H, (CH₃)₂CCHOSi), 4.11 (dd, $J = 7.3, 5.7$ Hz, 1 H, CH₂CHOSi), 3.74 (dd, $J = 6.1, 1.8$ Hz, 1 H, CH(CH₃)CHOSi), 3.13 (dq, $J = 7.0, 6.5$ Hz, 1 H, C(O)CH(CH₃)), 2.70 (s, 3 H, N=C(CH₃)S), 2.44 (dd, $J = 16.4, 3.1$ Hz, 1 H, CH₂COOH), 2.31 (dd, $J = 16.4, 6.8$ Hz, 1 H, CH₂COOH), 2.28–2.04 (m, 3 H, CH₂C(CH₃)=CH, CH₂C(CH₃)=CHCH₂), 1.94 (s, 3 H, CH=C(CH₃)), 1.96–1.86 (m, 1 H), 1.66 (s, 3 H, CH₂C(CH₃)=CH), 1.47–1.31 (m, 4 H), 1.17 (s, 3 H, C(CH₃)₂), 1.12 (s, 3 H, C(CH₃)₂), 1.21–1.09 (m, 1 H), 1.08 (d, $J = 6.8$ Hz, 3 H, CH(CH₃)), 0.90–0.85 (m, 30 H, CH(CH₃), 3 \times SiC(CH₃)₃), 0.10 (s, 3 H, Si(CH₃)₂), 0.06 (s, 3 H, Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂), 0.03 (s, 3 H, Si(CH₃)₂), 0.02 (s, 3 H, Si(CH₃)₂), –0.02 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 218.2, 175.5, 165.0, 152.8, 143.4, 137.0, 121.6, 118.2, 114.5, 79.1, 73.1, 53.8, 44.4, 40.0, 39.2, 35.3, 32.4, 31.4, 26.2, 26.0, 25.8, 25.7, 23.5, 23.4, 18.8, 18.7, 18.4, 18.2, 16.8, 15.8, 13.9, –3.9, –4.0, –4.1, –4.6, –4.7, –5.0; FAB HRMS (NBA/CsI) m/e 984.4427, M + Cs⁺ calcd for C₄₃H₅₃NO₆SSi 984.4460. **12Z-Carboxylic acid 53:** $R_f = 0.65$ (silica gel, 5% MeOH in CH₂Cl₂); $[\alpha]_D^{20} +6.2$ (c 0.6, CHCl₃); IR (thin film) ν_{\max} 2933, 2854, 1708, 1459, 1386, 1249, 1074, 988, 830, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH₃), 5.12 (dd, $J = 7.4, 6.9$ Hz, 1 H, (CH₃)₂C=CHCH₂), 4.56 (dd, $J = 6.1, 5.6$ Hz, 1 H, (CH₃)₂CCHOSi), 4.07 (dd, $J = 7.6, 5.6$ Hz, 1 H, CH₂CHOSi), 3.85 (d, $J = 8.4$ Hz, 1 H, CH(CH₃)CHOSi), 3.10 (dq, $J = 7.1, 7.0$ Hz, 1 H, C(O)CH(CH₃)), 2.75 (s, 3 H, N=C(CH₃)S), 2.43–2.10 (m, 4 H), 1.96–1.88 (m, 2 H), 1.91 (s, 3 H, CH=C(CH₃)), 1.66 (s, 3 H, CH₂C(CH₃)=CH), 1.35–1.02 (m, 14 H, CH(CH₃), 2 \times CH₂, C(CH₃)₂, C(CH₃)₂, CH(CH₃)), 0.92–0.80 (m, 30 H, 3 \times SiC(CH₃)₃, CH(CH₃)), 0.09–0.01 (m, 18 H, 3 \times Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 218.1, 174.2, 165.4, 152.3, 143.7, 137.1, 121.6, 117.9, 114.4, 78.9, 72.4, 53.8, 45.8, 40.4, 38.3, 35.6, 35.3, 32.3, 26.7, 26.3, 26.2, 26.0, 25.8, 25.7, 23.9, 23.8, 18.6, 18.5, 18.4, 17.1, 13.9, 13.4, –3.4, –3.6, –4.3, –4.6, –4.7, –4.9; FAB HRMS (NBA/CsI) m/e 984.4430, M + Cs⁺ calcd for C₄₃H₅₃NO₆SSi 984.4460.

12Z-Hydroxy Acid 6. 12Z-Carboxylic acid 52 (400 mg, 0.47 mmol) was converted to 12Z-hydroxy acid 6 (253 mg, 73% yield) according to the same procedure described above for 5. **6:** yellow oil; $R_f = 0.41$ (silica gel, 5% MeOH in CH₂Cl₂); $[\alpha]_D^{20} -10.4$ (c 0.4, CHCl₃); IR (thin film) ν_{\max} 3227, 2933, 2852, 1711, 1696, 1468, 1387, 1245, 1189, 1087, 986, 834, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.95 (s, 1 H, SCH=C), 6.67 (s, 1 H, CH=CCH₃), 5.19 (dd, 1 H, $J = 7.5, 7.0$ Hz, CH₂C=CHCH₂), 4.41 (dd, $J = 6.0, 3.5$ Hz, 1 H, (CH₃)₂CCHOSi), 4.16 (dd, $J = 6.6, 6.5$ Hz, 1 H, CH₂CHOH), 3.78 (d, $J = 6.9$ Hz, 1 H, CH(CH₃)CHOSi), 3.13 (dq, $J = 6.9, 6.6$ Hz, 1 H, C(O)CHCH₃), 2.72 (s, 3 H, N=C(CH₃)S), 2.47 (dd, $J = 16.2, 3.9$ Hz, 1 H, CH₂COOH), 2.40–2.35 (m, 3 H, CH₂C(CH₃)=CH, CH₂COOH), 2.17–2.10 (m, 1 H, C(CH₃)=CHCH₂), 2.00 (s, 3 H, CH=C(CH₃)), 1.99–1.93 (m, 1 H, C(CH₃)=CHCH₂), 1.72 (s, 3 H, CH₂C(CH₃)=CH), 1.53–1.35 (m, 5 H), 1.19 (s, 3 H, C(CH₃)₂), 1.14 (s, 3 H, C(CH₃)₂), 1.07 (d, $J = 6.7$ Hz, 3 H, CH(CH₃)), 0.94–0.84 (m, 21 H, CH(CH₃), SiC(CH₃)₃), 0.11 (s, 3 H, Si(CH₃)₂), 0.07 (s, 6 H, Si(CH₃)₂), 0.05 (s, 3 H, Si(CH₃)₂); ¹³C NMR (125.7 MHz, CDCl₃) δ 217.9, 174.8, 165.1, 152.3, 142.1, 139.4, 120.2, 118.5, 115.0, 73.2, 53.8, 44.5, 40.0, 39.1, 34.1, 32.4, 31.2, 26.2, 26.1, 25.9, 23.5, 23.3, 18.9, 18.6, 18.3, 18.1, 16.8, 16.0, 14.6, –3.9, –4.1, –4.2, –4.7; FAB HRMS (NBA/CsI) m/e 870.3632, M + Cs⁺ calcd for C₃₉H₇₁NO₆SSi 870.3595.

Hydroxy Acid 67. 12Z-Carboxylic acid 53 (200 mg, 0.24 mmol) was converted to 12Z-hydroxy acid 67 (123 mg, 71% yield) according to the procedure described above for 5. **67:** yellow oil; $R_f = 0.45$ (silica gel, 5% MeOH in CH₂Cl₂); $[\alpha]_D^{20} -8.1$ (c 0.3, CHCl₃); IR (thin film) ν_{\max} 3227, 2933, 2862, 1711, 1691, 1463, 1382, 1250, 1189, 1082, 986, 834, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.96 (s, 1 H, SCH=C), 6.61 (s, 1 H, CH=CCH₃), 5.15 (dd, 1 H, $J = 7.5, 7.0$ Hz, CH₂C=CHCH₂), 4.55 (dd, $J = 6.1, 3.5$ Hz, 1 H, (CH₃)₂CCHOSi), 4.12 (dd, $J = 8.0, 4.5$ Hz, 1 H, CH₂CHOH), 3.86 (d, $J = 8.2$ Hz, 1 H, CH(CH₃)CHOSi), 3.12 (dq, $J = 7.2, 7.0$ Hz, 1 H, C(O)CHCH₃), 2.75 (s, 3 H, N=C(CH₃)S), 2.37–2.30 (m, 5 H, CH₂C(CH₃)=CH, CH₂COOH, C(CH₃)=CHCH₂), 1.98 (s, 3 H, CH=C(CH₃)), 1.94–1.89 (m,

1 H), 1.72 (s, 3 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.39–1.04 (m, 14 H, $\text{CH}(\text{CH}_3)$, $\text{CH}(\text{CH}_3)$, $2 \times \text{CH}_2$, $\text{C}(\text{CH}_3)_2$), 0.95–0.84 (m, 21 H, $\text{Si}(\text{CH}_3)_2$), $\text{CH}(\text{CH}_3)$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.08 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.07 (s, 6 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.6, 174.0, 165.6, 152.0, 142.4, 139.4, 120.1, 118.0, 114.7, 72.4, 53.8, 45.8, 40.4, 38.4, 35.5, 34.0, 32.1, 26.4, 26.2, 26.0, 25.9, 23.8, 23.6, 18.5, 18.4, 18.2, 17.2, 14.9, 13.2, -3.5, -3.7, -4.4, -4.8; FAB HRMS (NBA/CsI) *m/e* 870.3574, *M* + Cs^+ calcd for $\text{C}_{39}\text{H}_{71}\text{NO}_6\text{Si}_2$ 870.3595.

Lactone 54. Macrolactonization of 12Z-Hydroxy Acid 6. 12Z-Hydroxy acid 6 (8.1 mg, 0.011 mmol) was cyclized according to the procedure described above for 6' to afford lactone 54 (6.1 mg, 77%).

Lactone 68. Macrolactonization of 12Z-Hydroxy Acid 67. The macrolactonization of 12Z-hydroxy acid 67 (5.0 mg, 0.007 mmol) to lactone 68 (3.7 mg, 76%) was carried out according to the procedure described above for 6'. 68: colorless oil; R_f = 0.83 (silica gel, 2% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$ -31.8 (c 0.1, CHCl_3); IR (thin film) ν_{max} 2931, 2860, 1736, 1690, 1461, 1384, 1360, 1296, 1249, 1084, 985, 832, 773 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 6.98 (s, 1 H, $\text{SCH}=\text{C}$), 6.45 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.07–5.21 (m, 2 H, $\text{CH}_2\text{C}=\text{CHCH}_2$, CH_2COOCH), 4.32 (dd, J = 6.8, 5.0 Hz, 1 H, CHOSi), 4.05 (d, J = 5.7 Hz, 1 H, CHOSi), 3.17 (dq, J = 7.0, 6.8 Hz, 1 H, $\text{C}(\text{O})\text{CHCH}_3$), 2.70 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.57–2.52 (m, 1 H), 2.29 (dd, J = 14.4, 4.6 Hz, 1 H, CH_2COOCH), 2.27–2.13 (m, 1 H), 2.25 (dd, J = 14.5, 7.0 Hz, 1 H, CH_2COOCH), 2.20–2.15 (m, 2 H), 2.14 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.88–1.82 (m, 1 H), 1.57–1.52 (m, 1 H), 1.47–1.38 (m, 3 H), 1.30 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.11 (d, J = 7.2 Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.08 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 0.91 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.89–0.82 (bs, 12 H, $\text{Si}(\text{CH}_3)_3$), $\text{CH}(\text{CH}_3)$), 0.11 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.06 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), -0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (150.9 MHz, CDCl_3) δ 220.2, 170.9, 164.8, 153.1, 140.0, 137.6, 120.2, 118.9, 116.3, 79.3, 74.0, 53.3, 48.0, 47.2, 39.7, 34.9, 31.4, 31.3, 26.6, 26.1, 25.9, 25.3, 23.9, 19.0, 18.5, 18.4, 18.1, 16.2, 14.9, 13.8, -3.9, -4.4, -4.6, -4.9; FAB HRMS (NBA/CsI) *m/e* 852.3451, *M* + Cs^+ calcd for $\text{C}_{39}\text{H}_{69}\text{NO}_5\text{Si}_2$ 852.3489.

Ketone 69. To a solution of aldehyde 20 (1.3 g, 4.53 mol) in THF (20 mL) at -78°C was added dropwise lithium tri-*tert*-butoxyaluminumhydride (4.98 mL, 1.0 M solution in THF, 4.98 mmol, 1.1 equiv). After 5 min, the reaction mixture was brought up to 0°C and stirred at that temperature for 15 min, before quenching with saturated aqueous solution of sodium-potassium tartrate (25 mL). The aqueous phase was extracted with ether (3 \times 20 mL), and the combined organic layer was dried (MgSO_4), filtered, and concentrated. The crude primary alcohol so obtained was dissolved in CH_2Cl_2 (25 mL) and cooled to 0°C . Et_3N (2.5 mL, 15.85 mmol, 3.5 equiv), 4-DMAP (60 mg, 0.09 mmol, 0.02 equiv), and *tert*-butyldimethylsilyl chloride (2.0 g, 13.59 mmol, 3.0 equiv) were added. The reaction mixture was allowed to stir at 0°C for 2 h, then at 25°C for 10 h. MeOH (5 mL) was added, and the solvents were removed under reduced pressure. Ether (100 mL) was added followed by saturated aqueous NH_4Cl solution (25 mL), and the organic phase was separated. The aqueous phase was extracted with ether (2 \times 50 mL), and the combined organic solution was dried (MgSO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure bis(silyl ether) 69 (1.26 g, 70% yield from 20); R_f = 0.67 (silica gel, 20% ether in hexanes); $[\alpha]_D^{20}$ -7.3 (c 1.8, CHCl_3); IR (thin film) ν_{max} 2941, 2856, 1701, 1466, 1388, 1252, 1095, 1024, 946, 832, 775 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.06 (dd, J = 8.0, 3.0 Hz, 1 H, CHOSi), 3.65–3.56 (m, 2 H, CH_2OSi), 2.56 (dq, J = 18.5, 7.0 Hz, 1 H, CH_2CH_3), 2.46 (dq, J = 18.5, 7.0 Hz, 1 H, CH_2CH_3), 1.56–1.43 (m, 2 H, $\text{CH}_2\text{CH}_2\text{OSi}$), 1.11 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.04 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 0.98 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 0.88 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.09 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.02 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.5, 73.2, 59.9, 52.9, 37.1, 34.1, 25.9, 25.7, 22.0, 19.8, 18.2, 18.1, 7.6, -4.1, -4.2, -5.4, -5.5; FAB HRMS (NBA) *m/e* 403.3075, *M* + H^+ calcd for $\text{C}_{21}\text{H}_{46}\text{O}_3\text{Si}_2$ 403.3064.

Tris(silyl ethers) 70 and 71. Aldol Reaction of Ketone 69 with Aldehyde 8. A solution of ketone 68 (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (94 μL , 0.67 mmol) was added to *n*-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0°C] in THF (2.5 mL) at -78°C . After being stirred for 15 min at -78°C , the solution was allowed to warm to -40°C over a period of 1 h.

The reaction mixture was cooled to -78°C , and a solution of aldehyde 8 (244 mg, 0.56 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78°C and then quenched by dropwise addition of saturated aqueous NH_4Cl solution (2 mL). The aqueous phase was extracted with ether (3 \times 5 mL), and the combined organic layer was dried (MgSO_4) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products 70:71 (354 mg (85%)) of ca. 3:1 by ^1H NMR). Separation of these diastereoisomers was carried out by preparative thin-layer chromatography (silica gel, 20% ether in hexanes), leading to pure 70 (270 mg, 64%) and 71 (84 mg, 20%). 70: colorless oil; R_f = 0.40 (silica gel, 20% ether in hexanes); $[\alpha]_D^{20}$ -17.5 (c 0.5, CHCl_3); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.89 (s, 1 H, $\text{SCH}=\text{C}$), 6.44 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.12 (dd, J = 7.1, 7.0 Hz, 1 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 4.08 (dd, J = 6.8, 6.5 Hz, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 3.89 (dd, J = 7.6, 2.7 Hz, 1 H, CH_2CHOSi), 3.69–3.65 (m, 1 H, $\text{CH}(\text{CH}_3)\text{CHOH}$), 3.59 (t, J = 7.5 Hz, 2 H, CH_2OSi), 3.32–3.27 (m, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.68 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.30–2.19 (m, 2 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 2.10–1.90 (m, 2 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.98 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.65 (s, 3 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.80–1.46 (m, 5 H), 1.34–1.25 (m, 2 H), 1.19 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.07 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.01 (d, J = 6.8 Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.89 (s, 18 H, $2 \times \text{Si}(\text{CH}_3)_3$), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.81 (d, J = 6.8 Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.10 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.08 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.02 (s, 6 H, $\text{Si}(\text{CH}_3)_2$), -0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 222.0, 164.1, 153.1, 142.4, 136.7, 121.3, 118.5, 114.7, 78.9, 74.7, 74.0, 60.3, 53.8, 41.2, 37.7, 35.9, 32.8, 32.5, 32.2, 26.0, 25.9, 25.8, 25.0, 24.9, 23.5, 22.8, 20.4, 19.0, 18.2, 18.1, 18.0, 15.2, 13.8, 9.5, -3.8, -4.2, -4.8, -5.1, -5.4; FAB HRMS (NBA/CsI) *m/e* 970.4620, *M* + Cs^+ calcd for $\text{C}_{45}\text{H}_{87}\text{NO}_5\text{Si}_3$ 970.4667. 71: colorless oil; R_f = 0.33 (silica gel, 20% ether in hexanes); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.90 (s, 1 H, $\text{SCH}=\text{C}$), 6.44 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.16–5.12 (m, 1 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 4.09–4.05 (m, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 3.65–3.58 (m, 3 H, CH_2CHOSi , CH_2OSi), 3.42–3.38 (m, 1 H, $\text{CH}(\text{CH}_3)\text{CHOH}$), 3.24–3.19 (m, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.69 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.31–2.18 (m, 2 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.98 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.99–1.88 (m, 2 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.67 (s, 3 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.55–1.40 (m, 5 H), 1.35–1.25 (m, 2 H), 1.20 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.13 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.09 (d, J = 7.0 Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.95 (d, J = 7.0 Hz, 3 H, $\text{CH}(\text{CH}_3)$), 0.88 (s, 18 H, $2 \times \text{Si}(\text{CH}_3)_3$), 0.87 (s, 9 H, $\text{Si}(\text{CH}_3)_3$), 0.10 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.05 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 6 H, $\text{Si}(\text{CH}_3)_2$), -0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); FAB HRMS (NBA) *m/e* 838.5653, *M* + Cs^+ calcd for $\text{C}_{45}\text{H}_{87}\text{NO}_5\text{Si}_3$ 838.5691.

Tetrakis(silyl ether) 72. Compound 70 (275 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (5.0 mL), cooled to 0°C , and treated with 2,6-lutidine (76 μL , 0.66 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (88 μL , 0.39 mmol, 1.2 equiv). After being stirred for 2 h at 0°C , the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N solution) and the aqueous phase was extracted with CH_2Cl_2 (3 \times 5 mL). The combined organic solution was washed with brine (5 mL), dried (MgSO_4), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetrakis(silyl ether) 72 (300 mg, 96%) as a colorless oil. 72: R_f = 0.56 (silica gel, 10% ether in hexanes); $[\alpha]_D^{20}$ -10.8 (c 0.5, CHCl_3); IR (thin film) ν_{max} 2919, 2872, 1690, 1461, 1384, 1361, 1249, 1085, 985, 838, 773, 732, 667 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.88 (s, 1 H, $\text{SCH}=\text{C}$), 6.43 (s, 1 H, $\text{CH}=\text{CCH}_3$), 5.13 (dd, J = 7.1, 7.0 Hz, 1 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 4.08 (dd, J = 6.8, 6.7 Hz, 1 H, $(\text{CH}_3)_2\text{CCHOSi}$), 3.89 (dd, J = 7.6, 2.7 Hz, 1 H, CH_2CHOSi), 3.77 (dd, J = 6.7, 1.0 Hz, 1 H, $\text{CH}(\text{CH}_3)\text{CHOH}$), 3.67–3.62 (m, 1 H, CH_2OSi), 3.58–3.53 (m, 1 H, CH_2OSi), 3.14 (dd, J = 6.8, 6.7 Hz, 1 H, $\text{C}(\text{O})\text{CH}(\text{CH}_3)$), 2.68 (s, 3 H, $\text{N}=\text{C}(\text{CH}_3)\text{S}$), 2.29–2.17 (m, 2 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.98 (s, 3 H, $\text{CH}=\text{C}(\text{CH}_3)$), 1.97–1.89 (m, 2 H, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$), 1.64 (s, 3 H, $\text{C}(\text{CH}_3)=\text{CHCH}_2$), 1.50–1.45 (m, 5 H), 1.34–1.23 (m, 2 H), 1.20 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 1.02 (d, J = 6.8 Hz, 3 H, $\text{CH}(\text{CH}_3)$), 1.00 (s, 3 H, $\text{C}(\text{CH}_3)_2$), 0.88–0.86 (m, 39 H, $\text{CH}(\text{CH}_3)$, $4 \times \text{Si}(\text{CH}_3)_3$), 0.08 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.07 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.04 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.03 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), 0.02 (s, 6 H, $\text{Si}(\text{CH}_3)_2$), 0.01 (s, 3 H, $\text{Si}(\text{CH}_3)_2$), -0.02 (s, 3 H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.2, 164.2, 153.2, 142.4, 136.6, 121.5, 118.5, 114.9,

78.8, 77.3, 73.9, 60.9, 53.6, 44.9, 38.8, 37.9, 35.2, 32.4, 30.9, 26.2, 26.1, 25.9, 24.4, 23.4, 19.2, 19.1, 18.5, 18.3, 18.2, 18.1, 17.5, 13.9, -3.7, -3.8, -4.0, -4.7, -4.9, -5.2, -5.3; FAB HRMS (NBA) *m/e* 952.6515. $M + H^+$ calcd for $C_{51}H_{101}NO_5SSi_4$ 952.6556.

Alcohol 73. Alcohol 73 (200 mg, 85%) was obtained from compound 72 (264 mg, 0.28 mmol) according to the procedure described above for 35. 73: colorless oil; $R_f = 0.25$ (silica gel, 20% ether in hexanes); $[\alpha]_D^{25} -9.3$ (c 0.2, $CHCl_3$); IR (thin film) ν_{max} 3392, 2939, 2865, 1689, 1463, 1378, 1357, 1252, 1083, 988, 867, 835, 772, 730 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1 H, $SCH=C$), 6.44 (s, 1 H, $CH=CCH_3$), 5.14 (dd, $J = 7.0, 6.9$ Hz, 1 H, $C(CH_3)=CHCH_2$), 4.10–4.05 (m, 2 H, $(CH_3)_2CCHOSi$, CH_2CHOSi), 3.78 (dd, $J = 7.0, 1.0$ Hz, 1 H, $CH(CH_3)CHOSi$), 3.63 (t, $J = 7.0$ Hz, 2 H, CH_2OH), 3.11 (dd, $J = 7.0, 6.8$ Hz, 1 H, $C(O)CH(CH_3)$), 2.70 (s, 3 H, $N=C(CH_3)S$), 2.27–2.19 (m, 2 H, $C(CH_3)=CHCH_2$), 1.99 (d, $J = 1.0$ Hz, 3 H, $CH=C(CH_3)$), 2.10–1.90 (m, 2 H, $CH_2C(CH_3)=CH$), 1.65 (s, 3 H, $C(CH_3)=CHCH_2$), 1.50–1.39 (m, 2 H), 1.36–1.29 (m, 3 H), 1.21 (s, 3 H, $C(CH_3)_2$), 1.20–1.10 (m, 2 H), 1.05 (s, 3 H, $C(CH_3)_2$), 1.04 (d, $J = 6.8$ Hz, 3 H, $CH(CH_3)$), 0.91–0.87 (m, 30 H, $CH(CH_3)$), 3 \times $Si(CH_3)_3$, 0.11 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 6 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), -0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 219.5, 164.2, 153.1, 142.4, 136.6, 121.5, 118.5, 114.8, 78.8, 77.4, 72.9, 60.1, 53.6, 45.8, 44.9, 38.6, 38.2, 35.2, 32.4, 30.6, 26.1, 25.9, 24.7, 23.4, 19.1, 18.4, 18.1, 18.0, 17.6, 15.5, 13.8, -3.7, -3.8, -4.0, -4.7, -5.1; FAB HRMS (NBA/ CS_2) *m/e* 970.4694. $M + Cs^+$ calcd for $C_{45}H_{87}NO_5SSi_3$ 970.4667.

Aldehyde 74. Oxidation of Alcohol 73. To a solution of oxalyl chloride (54 μ L, 0.61 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) was added dropwise DMSO (86 μ L, 1.21 mmol, 4.0 equiv) at $-78^\circ C$. After the mixture was stirred for 15 min at $-78^\circ C$, a solution of alcohol 73 (255 mg, 0.305 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added dropwise at $-78^\circ C$ over a period of 5 min. The solution was stirred at $-78^\circ C$ for 30 min, and then Et_3N (250 μ L, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to $0^\circ C$ over a period of 30 min, and then ether (20 mL) was added, followed by saturated aqueous NH_4Cl solution (10 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 \times 10 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde 74 (241 mg, 95%) as a colorless oil. 74: $R_f = 0.47$ (silica gel, 20% ether in hexanes); $[\alpha]_D^{25} -12.0$ (c 0.1, $CHCl_3$); IR (thin film) ν_{max} 2943, 2849, 1725, 1690, 1461, 1384, 1249, 1079, 985, 832, 773 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 9.74 (m, 1 H, CHO), 6.89 (s, 1 H, $SCH=C$), 6.43 (s, 1 H, $CH=CCH_3$), 5.14 (dd, $J = 7.1, 7.0$ Hz, 1 H,

$C(CH_3)=CHCH_2$), 4.48–4.44 (m, 1 H, $(CH_3)_2CCHOSi$), 4.07 (dd, $J = 6.1, 5.3$ Hz, 1 H, CH_2CHOSi), 3.75 (dd, $J = 7.4, 1.0$ Hz, 1 H, $CH(CH_3)CHOSi$), 3.11 (dd, $J = 7.0, 6.7$ Hz, 1 H, $C(O)CH(CH_3)$), 2.69 (s, 3 H, $N=C(CH_3)S$), 2.50 (ddd, $J = 16.6, 4.5, 1.0$ Hz, 1 H, CH_2CHO), 2.37 (ddd, $J = 16.6, 3.2, 1.0$ Hz, 1 H, CH_2CHO), 2.28–2.16 (m, 2 H, $C(CH_3)=CHCH_2$), 1.97 (s, 3 H, $CH=C(CH_3)$), 1.97–1.89 (m, 2 H, $CH_2C(CH_3)=CH$), 1.64 (s, 3 H, $C(CH_3)=CHCH_2$), 1.50–1.25 (m, 5 H), 1.22 (s, 3 H, $C(CH_3)_2$), 1.05 (s, 3 H, $C(CH_3)_2$), 1.01 (d, $J = 6.9$ Hz, 3 H, $CH(CH_3)$), 0.89–0.84 (m, 30 H, $CH(CH_3)$), 3 \times $Si(CH_3)_3$, 0.08 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 6 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 3 H, $Si(CH_3)_2$), -0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.5, 201.0, 164.3, 153.2, 142.7, 136.7, 121.5, 118.5, 114.8, 78.9, 77.7, 71.3, 53.4, 45.1, 38.7, 35.3, 32.5, 30.7, 26.2, 25.9, 25.8, 24.1, 23.5, 19.1, 18.7, 18.6, 18.5, 17.7, 15.6, 13.9, -3.6, -3.7, -4.1, -4.5, -4.7, -5.0; FAB HRMS (NBA) *m/e* 836.5500. $M + H^+$ calcd for $C_{45}H_{85}NO_5SSi_3$ 836.5535.

Carboxylic Acid 52. Oxidation of Aldehyde 74. Aldehyde 74 (224 mg, 0.29 mmol), t -BuOH (5.0 mL), isobutylene (5.0 mL, 2 M solution in THF, 10.0 mmol), H_2O (1.0 mL), $NaClO_2$ (90 mg, 0.86 mmol, 3.0 equiv), and NaH_2PO_4 (60 mg, 0.43 mmol, 1.5 equiv) were combined and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) to afford carboxylic acid 52 (220 mg, 90%) whose spectroscopic data were identical with those exhibited by 52 obtained above.

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Supporting Information Available: Selected physical data for compounds 48, 49, 8', 52', 53', and 6' and 1H – 1H NOESY and 1H – 1H COSY spectra for epoxides 58 and 59 (8 pages). See any current masthead page for ordering and Internet access instructions.

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